Great Beginnings for Healthy Native Smiles: An Early Childhood Caries Prevention Project

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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.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name:

Title:

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CAB	Community Advisory Board
CFR	Code of Federal Regulations
CHR	Community Health Representative
CSI	Clinical Site Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DHHS	Department of Health and Human Services
DMFS	Decayed, missing, and filled tooth surfaces
DMFT	Decayed, missing, and filled teeth
DSMB	Data and Safety Monitoring Board
ECC	Early Childhood Caries
FDA	Food and Drug Administration
FFR	Federal Financial Report
FV	Fluoride Varnish
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IHS	Indian Health Service
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NAU	Northern Arizona University
NIDCR	National Institute of Dental and Craniofacial Research, NIH, DHHS
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
PO	Program Official, NIDCR, NIH
PS	Project Scientist, NIDCR, NIH

QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

PROTOCOL SUMMARY

Title: Great Beginnings for Healthy Native Smiles: An Early Childhood Caries Prevention Project.

Précis: Early Childhood Caries (ECC) is the most common chronic disease among children. American Indian (AI) children are 4 times more likely to have untreated dental decay than white children. This is a four year parallel group randomized clinical trial evaluating the impact of a bundled best practices oral health intervention on early childhood caries in American Indian children as indicated by the number of decayed, missing and/or filled primary tooth surfaces (dmfs). The intervention is delivered during pregnancy and through child age 24-36 months. The bundled best practices include motivational interviewing with mothers and fluoride varnish applied to the child's teeth. The oral health intervention also includes Tribe-specific individual, social and health needs identified in an earlier formative assessment. The oral health intervention group (n=175 mother-child dyads) will be compared to a group (n=175 mother-child dyads) receiving a standard prenatal/postnatal healthy lifestyle intervention. All study treatments will be delivered by Community Health Representatives in the Hopi (Arizona) and Crow (Montana) communities. Children will be followed until 2 - 3 years of age.

Objectives:

Primary Objective: To determine whether children in the OH group compared to the Healthy Lifestyle group have on average fewer decayed, missing and/or filled primary tooth surfaces (dmfs) measured at the last visit.

Secondary Objective 1: To determine whether children in the OH group compared to the Healthy Lifestyle group have on average fewer decayed missing or filled teeth (dmft) measured at the last visit.

Secondary Objectives 2-4: To examine if women in the OH group compared to the Healthy Lifestyle group have greater increases in:

- Oral health knowledge
- Oral health behavior
- Positive attitudes towards oral health care

These will be compared as changes from baseline (Visit 1) to the last (Visit 6) survey assessment.

Secondary Objective 5: To examine if women in the Healthy Lifestyle group compared to the OH group have greater increases in knowledge of developmental milestones, pregnancy related nutrition, breastfeeding and prenatal health at Visit 6 relative to baseline (Visit 1).

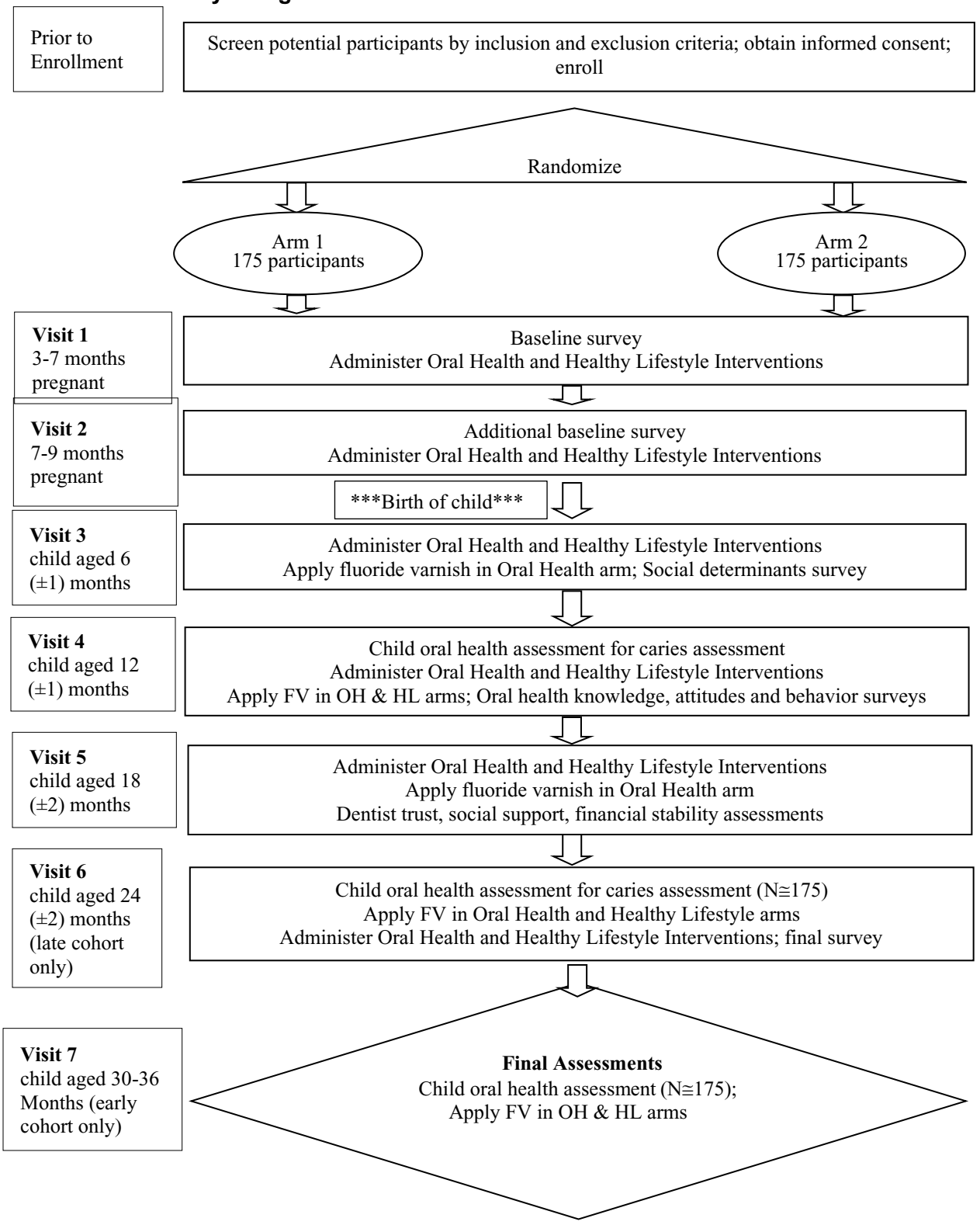
Population: Healthy pregnant women who are American Indian (AI) or giving birth to an AI child on or near the Hopi and Crow Nations in Arizona and Montana, respectively, and their infants, once born.

Phase or Stage: Not applicable

Number of Sites: Study activities will take place at WIC and Head Start centers in two locations, the Hopi Nation in Arizona and the Crow Nation in Montana. The study will be overseen by three IRBs-Northern Arizona University, Phoenix Area IHS and the Rocky Mountain Tribal IRB.

Description of Intervention:	The Oral Health intervention for pregnant women/new mothers in the oral health intervention group will include motivational interviewing and oral health education intended to protect their children from ECC. They may receive care-coordination assistance in obtaining preventive and therapeutic oral health care for mother and newborn/infant. Newborn/infant participants will receive oral health interventions, fluoride varnish up to four times and oral health care referral where indicated. The Healthy Lifestyle intervention will provide pregnant women/new mothers with a standard prenatal/postnatal education curriculum which includes educational material from the National Head Start curriculum. The Healthy Lifestyle intervention educates women on nutrition and diet, physical activity, breastfeeding/formula feeding, substance use, mental/emotional health, personal and family goals, prenatal/postpartum health care access, labor and delivery, family support, infant/child care, oral health, and development milestones. Because of the high ECC risk environment, fluoride varnish will also be applied to children in the Healthy Lifestyle group at 12 and 24 months of age and receive oral health care referral where indicated. Community Health Representatives will deliver the treatments to both groups.
Study Duration:	Four years.
Subject Participation Duration:	Participation duration is 29 (late cohort) to 41 (early cohort) months depending on whether enrolled in the first or second half of recruitment.
Estimated Time to Complete Enrollment:	Approximately 14 months.

Schematic of Study Design:



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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Early Childhood Caries (ECC) is the most common chronic disease among children. American Indian (AI) children are 4 times more likely to have untreated dental decay than white children. If left untreated, ECC can lead to chronic pain, loss of teeth, poor nutrition, and impaired growth. This project aims to reduce the burden of ECC in two AI communities through a community based participatory approach. Previously we partnered with 2 tribes, the Hopi Tribe (Arizona) and the Crow Tribe (Montana) to conduct a formative assessment on oral health (OH). From this work the present study adapted a "bundled" best practices OH intervention to be locally and contextually relevant for each of the tribal communities. This protocol describes a randomized, controlled trial to evaluate the impact of the "bundled" best practices OH intervention (compared to a prenatal/postnatal healthy lifestyle intervention) on the reduction of ECC across these communities.

Two rigorous randomized trials in American Indian communities did not reduce ECC. A trial of Navajo children aged 3-5 years old included personalized oral health interactions for children and parents as well as fluoride varnish applications for children. Although caregiver knowledge and oral health behavior improved there was no difference in caries increment or prevalence at follow up.[1] Caries prevalence was almost universal by three years of age in this study, illustrating the substantial ECC burden in AI children and indicating that earlier intervention is desirable. A second trial[2] recruited pregnant AI women and compared enhanced community services to enhanced services plus motivational interviewing. Despite reasonable adherence and initiating the intervention shortly after birth, no caries differences were observed after 3 years of follow up.

However, an Australian clinical trial indicates that the combination of early intervention and fluoride varnish application may be effective in preventing caries among very young children in indigenous settings.[3] Jamieson et al. enrolled pregnant aboriginal Australian women.[3] The active treatment arm included motivational interviewing for caregivers and fluoride varnish application for children aged 6 to 24 months. This treatment combination resulted in fewer decayed teeth in two year old children compared to a usual care control group (means of 0.62 teeth [95%CI 0.59, 0.65] versus 0.89 [95%CI 0.85, 0.92], respectively).

Together these studies suggest that to prevent caries in indigenous children, interventions should a) start at birth before caries develop; b) utilize behavioral strategies such as motivational interviewing; and c) complement behavioral strategies with fluoride varnish application. The present study will recruit expectant mothers in two AI communities (Hopi and Crow) and utilize both motivational interviewing and multiple fluoride varnish applications (at 6, 12, 18 and 24+ months of age) to reduce ECC. This Oral Health intervention will include prenatal education regarding oral hygiene practices,

oral health screening and referral for children and fluoride varnish application every 6 months. These treatments are provided by community health representatives who incorporate locally and contextually relevant strategies for ECC prevention and use AI community members to implement the intervention. Contextually relevant strategies were identified in a formative assessment of each community prior to clinical trial enrollment.

2.2 Rationale

Sixty percent of American Indian children have dental caries by the age of three.[4] Small, rural tribal communities in particular have numerous obstacles to good oral health including long distances to services, low support for caregivers and limited resources. In partnership with the Hopi and Crow tribes we will implement an oral health intervention in these two communities. Although childhood oral health interventions have occurred among other western tribal communities, no such interventions have occurred within Hopi and Crow communities.

To date, best intervention practices include intervening during pregnancy - a time when expectant mothers are learning about dietary and other health promoting practices which align with and complement oral health promoting practices. Qualitative interviews of oral health care providers, expectant mothers and reproductive health services providers in each tribal community identified barriers and resources for caregiving, oral health care and community-level resources. This formative assessment, in turn, provides the foundation for culturally specific intervention materials. Motivational interviewing (MI), an individualized approach to guiding health behavior change, will be used to improve the capacity of caregivers to build self-efficacy, enact behavior change, and positively impact the OH of their children. Using MI to reduce ECC prevalence is recommended by the American Academy of Pediatric Dentistry.[5] The intervention will explicitly incorporate interpersonal level inputs (practices of other mothers in the community; family member expectations), community level inputs (e.g., requirements and supports provided by social service organizations); and key values within the larger society regarding the health and wellbeing of infants and toddlers (societal level). Locally recruited community health representatives will enact the intervention and provide instrumental support (signing children up for OH services), informational support (referring women to needed social services), and appraisal support (providing positive reinforcement when the mother/caregiver is able to successfully adhere to their child's OH appointments).

This approach is consistent with evidence showing that childhood caries prevention efforts among indigenous populations are most effective when targeting the expectant mother before birth and continuing treatment through the child's first tooth eruption.[3] This early treatment is optimized by motivational interviewing, individual and community support and the application of fluoride varnish to primary teeth. In contrast, interventions with indigenous communities that start later in childhood (ages 3-4)[1] or that do not incorporate fluoride varnish have not been effective in reducing early childhood caries.

Thus the present study will combine the most potent interventional approaches at the optimal stage of the child's oral health-before the child is born.

The comparison group will receive a "healthy lifestyle" maternal and child health intervention. This intervention will approximately match the contact duration of the oral health care arm and will cover prenatal care, maternal self-care, developmental milestones, infant nutrition, identifying food allergies, breastfeeding, and strategies to manage work and family demands. Thus, this comparison arm will comprise beneficial non-oral health related education and support for the comparison group. Although this treatment includes a brief oral health component it does not have oral health as its main focus.

We hypothesize that children in the oral health treatment arm will have fewer caries surfaces (dmfs) at 24-36 months old compared to the healthy lifestyle group.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

There are no known risks to any of the recommended oral hygiene practices, which all follow established guidelines in pediatric dentistry. There is a risk of disclosure of confidential information, including oral health status, extent of oral disease, and oral health behavioral information. Study processes intended to maintain data confidentiality are described in Section 16.1.

There is also the possibility of psychological distress associated with the oral assessment and the MI intervention. Participants will be asked some personal questions pertaining to their children and their daily oral health habits which could cause some distress. Mothers will have the opportunity to terminate their involvement in the study at any time and/or decline to respond to any questions.

The oral health treatment arm includes up to four fluoride varnish applications and children in the healthy lifestyle group will receive fluoride varnish at 12 and 24 months of age. Early cohort enrollees will receive another application at Visit 7. A review of three clinical trials where children received an average of four varnish treatments found zero (0) fluoride varnish related adverse events.[6] Despite the low potential risk of allergic reaction to FV we will withdraw children if they have ulcerative gingivitis or stomatitis or known sensitivity to colophony or other FV ingredients. Study staff will monitor participants for allergic reactions to the fluoride varnish.

Potential risks of educational interventions are low. Children in the healthy lifestyle group will not receive focused oral health information (although the mother will receive a short module related to oral health). The latter is not a risk per se but represents the absence of a potentially beneficial treatment in that group.

2.3.2 Potential Benefits

Participants in the oral health intervention arm will receive potentially useful information about maintaining good oral health. If the bundled best practices intervention demonstrates efficacy, children in that arm may have fewer decayed tooth surfaces than they would without the intervention. Participants in the healthy lifestyle arm will receive a number of potentially useful exposures including information regarding maternal self-care, identifying appropriate developmental milestones for their infant/child, as well as two FV applications. Information learned in this study could ultimately be beneficial to AI communities experiencing a high burden of ECC.

3 OBJECTIVES AND OUTCOME MEASURES

3.1 Primary

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
To determine whether children in the OH group compared to the Healthy Lifestyle group have on average fewer decayed, missing and/or filled primary tooth surfaces (dmfs) measured at the last visit	The primary outcome measure is the number of decayed, missing and/or filled primary tooth surfaces (dmfs). It was chosen as the primary outcome measure because dmfs is a direct measure of disease and is a clinical standard for assessing caries. Differences in dmfs scores across treatment groups will indicate less disease.	Indian Health Service dentists and/or trained hygienists (masked to treatment group, calibrated) will visually inspect every tooth in children in both treatment groups and indicate any decayed, missing, or filled surfaces (dmfs).	We will compare treatment group differences from the last follow up oral health assessment (either 24 months [late cohort] or 30-36 months [early cohort]). Differential follow up rationale and description in Section 12.

3.2 Secondary

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
To determine whether children in the OH group compared to the Healthy Lifestyle group have on average fewer decayed, missing and/or filled primary teeth (dmft) measured at the last visit	The number of decayed missing or filled teeth (dmft) complements the tooth surface assessment and provides a bridge assessment to compare with other oral health literature.	The dmfs scores will be converted to binary values for each tooth. Caries experience is defined by a dmfs score greater than 1 for each tooth. The number of teeth with caries is summed for each child.	We will compare treatment group differences from the last follow up oral health assessment (either 24 months [late cohort] or 30-36 months [early cohort]). Differential follow up rationale and description in Section 12.
To determine whether mothers/caregivers in the OH group compared to the Healthy Lifestyle group show increases in oral health knowledge	Oral health knowledge is a target of the intervention and will provide a benchmark for the oral health manipulation.	We will assess oral health knowledge with a 20-item assessment that includes a decoy item and two filler items. Source items come from the BRFQ survey and will be scored as a percent correct, excluding the filler items.	This outcome is measured at baseline (Visit 1; while expecting), after the child is 12 months of age (Visit 4) and each visit until the child is 24 months (Visits 5 & 6).

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
To determine whether mothers/caregivers in the OH group compared to the Healthy Lifestyle group perform more of the optimal care practices for their child's teeth (oral health behavior)	Optimal oral health care is reflected in the oral health behavior survey items (e.g., regular checking of teeth/gums; use of fluoride toothpaste; avoiding sugary food and drink; caregiver brushing frequency). These care behaviors are inversely correlated with childhood dmfs scores[7] and may reflect a treatment pathway.	We will assess oral health behavior with a 16-item assessment adapted from the BRFQ and prior studies of AI infants/children. Responses will be scored as the percent of responses with "adherent" or optimal oral health behavior.	This outcome is measured after the child is 12 months of age (Visit 4), 18 months of age (Visit 5) and again at child age 24 months (Visit 6).
To determine whether mothers/caregivers in the OH group compared to the Healthy Lifestyle group show more favorable attitudes towards oral health care	Attitudes towards desirable oral health behavior should change following the intervention and may track with intervention efficacy.	Attitudes are measured using 14 items that parallel the behavior questions (e.g., How important is it to you to check teeth/gums every month?). A sum of Likert-style ratings will comprise the attitudes These items are labeled "motivation" in the BRFQ instrument.	This outcome is measured at baseline (Visit 1; while expecting), after the child is 12 months of age (Visit 4) and again at child age 24 months (Visit 6).
To determine whether mothers/caregivers in the Healthy Lifestyle group compared to the OH group show increases in maternal/child health knowledge (non-oral health)	Maternal/child health knowledge is a target of the comparison group treatment and will be assessed to compare this knowledge across the two study groups.	We will assess maternal/child health knowledge with a 20-item assessment. Source items come from the Healthy Lifestyle modules and will be scored as a percent correct, excluding the filler items.	This outcome is measured at baseline (Visit 1; while expecting), after the child is 12 months of age (Visit 4) and each visit until the child is 24 months (Visits 5 & 6).

4 STUDY DESIGN

The study is a two group parallel randomized trial. There are two study sites but the study is overseen at Northern Arizona University in Flagstaff, AZ. Only the primary outcomes assessors are masked. For this trial both participants and the community health representatives providing the interventions will be aware of treatments received.

The study population is expectant mothers on the Hopi (AZ) and Crow (MT) Nations, and their infants, once born. These women will receive either 1) a bundled best practices oral health intervention including motivational interviewing and fluoride varnish application to their children's teeth beginning at 6 months of age (N=175 dyads) or 2) a "healthy lifestyle" intervention that focuses on maternal/child health, the peripartum period, nutrition, breastfeeding, etc. (N=175 dyads). This population was selected because of the extremely high burden of caries among American Indian children. Mothers will be recruited at 3-7 months gestation and followed through their child's second birthday (late cohort) or up to the child's third birthday (early cohort). Later follow up of approximately half of the enrolled children and mothers/caregivers (early cohort) is to increase statistical sensitivity for the intervention (see Section 12 Statistical Considerations). Mothers will be in the study from 29-41 months. After the first enrollee we anticipate 12-14 months of enrollment thereafter to achieve our target sample size.

The oral health arm will receive motivational interviewing treatment to improve knowledge, attitudes and behavior towards maternal and child oral health. Motivational interviewing tailors treatment to participant preferences and motivations. Motivational interviewing will be implemented by community health representatives (CHR) using a culturally informed treatment approach. Six motivational interviewing sessions are scheduled for the oral health treatment arm; two prior to giving birth and four more when the child is 6, 12, 18 and 24-27 months of age. The dose schedule has no planned variation. Motivational interviewing permits participant choice of topics within a set and thus it is likely that some oral health treatment arm participants will complete different subsets of MI topic areas. This variation is not considered a threat to study efficacy. Children in the oral health arm will receive fluoride varnish applications at ages 6, 12, 18, and 24 months.

The healthy lifestyle intervention will provide education and support for mothers regarding pregnancy, postpartum challenges, food preparation for children 12 months and older, infant nutrition, and parenting. This also includes a short module on oral health. The intervention will be administered by trained CHRs. Six sessions are scheduled for the healthy lifestyle group, with timing parallel to the timing of sessions in the oral health arm. Children in this arm will receive a fluoride varnish application by study staff at 12 months and 24 months. Children in the HL arm in the early cohort will receive a third FV application after their final study visit at child age 30-36 months.

Children in both groups will be scheduled for a full oral health assessment at 12 (Visit 4) and 24-27 months (Visit 6). Earlier recruits (through month 8 recruitment) will be followed up longer for a final oral assessment (Visit 7 at 30-36 months of age).

Assessments will be conducted by calibrated dentists and/or hygienists, masked to the study condition. Mothers will be reminded of their appointments through follow-up phone calls and/or in person visits from the Community Health Representatives. Dentists will provide oral assessment data to study staff who will securely upload the data into REDCap and securely store the records.

Secondary outcomes of oral health knowledge, behaviors, and attitudes and knowledge of maternal and child health issues not related to oral health will be assessed using questionnaires. Oral health knowledge and maternal child health knowledge will be assessed at Visits 1, 4, 5 and 6. Oral health attitudes will be assessed at Visits 1, 4 and 6 and oral health behavior will be assessed at Visits 4, 5 and 6. Survey data will be securely collected via laptop or tablet using REDCap software.

5 STUDY POPULATION

5.1 Participant Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provide signed and dated informed consent form
2. Be willing and able to follow study procedures and instructions and be available for the duration of the study
3. Be at least 18 years of age
4. Be American Indian or giving birth to an AI child, and living on or near (approximately 100 miles) the Hopi or Crow Nations. American Indian status is self-identified-no tribal enrollment verification will be required.
5. Be currently pregnant—preferably in month 4 of pregnancy at enrollment but mothers are eligible when 3-7 months pregnant (9-31 weeks pregnant).
6. Be willing to participate until the child is age 3
7. Mothers of twins will be included, but only one child will be enrolled as the study child.

5.2 Participant Exclusion Criteria

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

- Anything that would place the individual at increased risk or preclude the individual's full compliance with, or completion of, the study.
- Enrolled in other community health interventions that incorporate oral health intervention, e.g., Family Spirit program at Hopi.
- A member of the Northern Cheyenne Tribe
- Living on the Navajo Nation and a member of the Navajo Tribe

5.3 Strategies for Recruitment and Retention

Methods for recruitment include flyers, face to face, and referral phone calls.

Project staff will collaborate with IHS facilities, WIC clinic and Head Start (at Hopi) staff to identify pregnant women who meet inclusion criteria. At Crow we will recruit using community partners and suggestions from the CAB. A total of 350 mother-child pairs will be enrolled over approximately 14 months and randomized into 1) OH intervention or 2)

HL comparison. Intervention and comparison groups will receive the same number (6) of intervention sessions (Table 3). Because of the monthly enrollment plan, we will have a range of final assessment time points for participating children (between 24-36 months of age). Extending follow up for early enrollees will increase our statistical power by permitting follow up from a minimum of 2 years (late cohort) to a maximum of 3 years of age (early cohort), averaging ~ 2.5 years (see Section 12). Recruitment challenges will be addressed by establishing an achievable recruitment target that reflects current birth rates in our study populations. For example, at Hopi, we will aim to recruit 7 out of 9 women who give birth each month; in the Crow community, we will aim to recruit 18 out of 23 women who give birth each month. Our field staff are tribal members and have deep and trusting relationships with community members which should maximize recruitment and retention. Following the approach of Batliner et al.[8] we will partner with local maternal and child health services to enhance study recruitment. Little Bighorn College and the Crow CAB will be our primary partners at Crow. At Hopi, staff from Early Intervention and Head Start will participate in Community Advisory Board (CAB) meetings. Eligible pregnant women will be invited to participate and after providing informed consent will be randomly assigned to the OH intervention or HL comparison condition.

Study staff will collect a minimum of three additional contacts for each consenting participant (three points of contact with a phone number and address). Study staff will call participants to remind them of scheduled sessions at two weeks prior, one week prior, and one day prior intervals. During the span of these reminder calls, if a scheduling conflict arises, there is more time to remedy the possible missed session. Study staff will reschedule the session at the earliest possible convenience for both the CHR and the participant. If the participant does not confirm the session appointment at the two week or one-week interval, study staff will begin to call the additional contacts requested at enrollment. Study staff will have a script they can follow for voicemail/text reminders. To keep a good rapport, study staff will send birthday cards for children during the duration of the study. During the consent process, participants will provide study staff their preferred method of contact and all methods of contact that they will allow study staff to conduct. Contact methods will include but are not limited to phone calls, text messages, email, voicemail, and social media.

Community Health Representatives/Health Educators

The CHRs for the duration of the study will be members of the communities where recruitment will occur. Because of the small communities and closeness of members of the communities, recruitment and retention will be easier. CHRs will attempt follow-up not only through the aforementioned phone calls, texts, email, social media, and voicemail but CHRs will also attempt to contact participants through home visits. Study staff will utilize private direct messaging when using social media channels.

Compensation schedule:

$ 25.00 gift card at Visit 1
$ 25.00 gift card at Visit 2
$ 25.00 gift card at Visit 3

$ 25.00 gift card at Visit 4
$ 25.00 gift card at Visit 5
$ 25.00 gift card at Visit 6 ($50 for late cohort)
$ 50.00 gift card at Visit 7 (early cohort only)

A very detailed call log will be created for each participant in a locked excel file only accessible by study staff. This call log will detail each call made to participants, what number was called, what day/time, and what was said or if the study staff left a message (and which message). If study staff call the additional points of contact, that will be noted in the call log. The conversation between study staff and the additional contact will be summarized in case follow-up needs to occur. Study staff will attempt to contact participants who were unreachable throughout the duration of the study. Participants will be considered lost to follow up if they cannot be scheduled for their final dental assessment, i.e., within two months of their last scheduled study visit (Visit 6 or 7 depending upon initial enrollment). We will not replace any lost or withdrawn participants.

5.4 Treatment Assignment Procedures

The study statistician will create computer generated randomized treatment group allocations for each site. These randomized permuted blocks will be uploaded into REDCap to provide treatment group assignment. Following eligibility screening and informed consent documentation study staff will authorize participants for enrollment. Following this authorization (in REDCap) participants will be officially enrolled in the study and the REDCap system will then assign the next computer generated treatment group allocation (within site) to one of the two treatment conditions. Participants will be assigned in a 1:1 ratio to Oral Health and Healthy Lifestyle treatment groups.

5.4.1 Randomization Procedures

Randomization codes will be generated by the study statistician. The randomization list containing treatment assignment codes will be retained by the study statistician and will not be accessible to study staff. This is an electronic document that will be uploaded into REDCap on NAU's secure server. Permuted blocks will prevent field staff from knowing what treatment the next participant will receive during the recruitment process and ensure approximately equal numbers of participants in each study arm at any given time during study enrollment.

No break of randomization codes is anticipated but if necessary could be done in collaboration with the study statistician. Separate permuted blocks will be generated for each of the two sites.

5.4.2 Masking Procedures

Due to the nature of the interventions, the CHRs cannot be masked in this study. However, the dentists/hygienists who perform the annual oral assessments for dmfs will

be masked to participants' intervention arm. Dental assessments will take place before the scheduled Visit.

5.5 Participant Withdrawal or Discontinuation from Study Procedures/Intervention

5.5.1 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. If a family has a child with an identifiable high needs condition at birth they may choose to withdraw as they may need to focus time on those needs.

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

Mother-child dyads may be withdrawn from the study if the child is born with congenital oral anomalies expected to adversely affect the development of primary teeth, ectodermal dysplasia, or diseases other than ECC that affect the dentition or oral mucosa upon examination. This includes children with ulcerative gingivitis, stomatitis or other conditions resulting in chronically disrupted or irritated oral mucosa as reported by parent/caregiver or documented by a dental professional.

Mother-child dyads may be withdrawn from the study if the study child is allergic to any of the components of the FV as reported by parent/caregiver

Participants will also be withdrawn if informed consent is withdrawn by the parent/guardian or if they move permanently from the area.

An investigator may discontinue an individual's participation in an intervention or withdraw an individual from the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

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

If the mother/caregiver wants to drop out of the study early, we will ask if they wish to stop the intervention or drop out of the study entirely. If they want to stop the intervention, we will ask if they are willing to continue to be followed without the intervention and permit additional caries assessment(s). The purpose of this is to collect sufficient data to be able to conduct a more robust intent-to-treat analysis.

If a mother/caregiver drops out of the study early and refuses additional follow-up, an early termination visit will be requested. If this request is accepted, a dmfs measure for the child will be obtained along with a questionnaire to the mother/caregiver about dental knowledge, attitudes, and behavior; psychological influences; other health and risk factors; other dental interventions received; and the reasons for early termination.

If the mother/caregiver wants to withdraw from the study entirely we will include their data to that point in the analyses. If the mother/caregiver wants to completely withdraw consent then that record will be excluded from all analyses, including the intention-to-treat analysis. All withdrawals and discontinuations will be recorded using the Case Report Form.

If a person other than the mother becomes the child's primary caregiver we will invite that person to participate so that the child may continue in the study. We would complete informed consent to enroll the new caregiver. Although we expect this to be rare, the advantage of maintaining the child's participation would outweigh the disadvantage of a caregiver that does not receive the full set of intervention sessions. Caregivers meeting inclusion criteria 1, 2, 3 and 6 in Section 5.1 would be eligible to enroll. Caregiver changes will be tracked and any study visits occurring prior to the change will be noted as missed interventions.

5.6 Premature Termination or Suspension of Study

We do not anticipate any circumstance that would necessitate premature termination or suspension of the study. The study will not yield any early outcomes that would indicate that it should be stopped prior to completion. Similar randomized trials were categorized as minimal risk, had good adherence to protocol requirements using similar methods and there were no adverse events.[6]

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 Julie Baldwin (PI) and the NIDCR and the Hopi and Crow Tribes. The principal investigator will also promptly inform the IRB and will provide the reason(s) for the termination or suspension.

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

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

6 STUDY INTERVENTION

6.1 Study Product Description

As part of the Oral Health intervention enrolled infants/children will receive fluoride varnish on all erupted teeth up to four times during the study. Children in the Healthy Lifestyle comparison group will receive fluoride varnish applications at 12 and 24 months of age and again at Visit 7 for the HL children in the early cohort.

3M™ Vanish™ is a 5% sodium fluoride white varnish with tri-calcium phosphate. After application the varnish combines with saliva to release calcium and fluoride which combine to enhance the mineral content of saliva need to form tooth mineral. Tooth surfaces do not require cleaning before varnish application. Fluoride varnish is associated with a 37% reduction in decay of primary tooth surfaces.[9]

6.1.1 Acquisition

The fluoride varnish will be ordered from 3M and shipped to Northern Arizona University. NAU based staff will verify the quantities ordered, invoiced, and shipped and will forward the fluoride varnish from Flagstaff to the Crow and Hopi staff.

6.1.2 Formulation, Packaging, and Labeling

The clearly labeled box contains various quantities of 0.5ml unit dose packets with applicator brushes and patient instructions. Product information is included as **Appendix B**.

6.1.3 Product Storage and Stability

The fluoride varnish will be labeled and stored at the Hopi and Crow field offices in a locked cabinet. The manufacturer suggests storage in a “cool, dry place” (see **Appendix C**) so room temperature storage (between 10°C and 24°C; 50°F-75°F) should be satisfactory.

6.2 Dosage, Preparation and Administration of Study Product

The entire contents of the unit-dose package is dispensed onto a mixing surface, such as the gloved hand of the CHR. The dose is mixed using the applicator brush. Mixing is required because varnish components may separate during storage. A thin layer is applied with sweeping horizontal brush strokes onto the infant/child’s teeth. As per the manufacturer’s instructions applying fluoride varnish does not require drying teeth. It is not necessary to use all of the provided varnish-only enough to form a thin coating is required. As per manufacturer’s recommendations mothers/caregivers will be asked to refrain from cleaning their child’s teeth/mouth for 24 hours. The number and location of treated teeth will be recorded at each session.

CHRs will ask the mother/caregiver about fluoride supplements and if so, will be told to discontinue their use for 3 days following the FV application.

6.3 Modification of Study Product Administration for a Participant

Fluoride varnish will be dispensed in proportion to the number of erupted teeth. No other dosage modifications are anticipated.

6.4 Accountability Procedures for the Study Product

Inventory of fluoride varnish will be controlled using an inventory control form. Product lot numbers and expiration dates also will be tracked. Study staff involved in the administration of the fluoride varnish will sign out limited inventory prior to use and will return any un-used unit dose packages after fluoride varnish administration sessions are completed. The field office will maintain and periodically submit to the Project Coordinator records of fluoride varnish units in inventory and signed out to the study intervention personnel. These records will be audited biannually.

6.5 Assessment of Participant Compliance with Study Product Administration

The CHRs will be trained in the application of fluoride varnish according to the manufacturer's instructions. The CHRs will practice this skill during their initial training and will be evaluated for competency at the conclusion of their training. Data collection forms and visit windows will be used to standardize the delivery of FV throughout the intervention period. During the training period a dental hygienist member of the study team will show the CHR how to apply FV and observe each CHR applying FV to at least two people.

6.6 Study Behavioral or Social Intervention(s) Description

6.6.1 Oral Health Intervention

The behavioral intervention for pregnant women/new mothers in the oral health intervention group will include:

- Motivational interviewing and support provided by CHRs. They will learn via oral health education to be better able to protect their children from ECC. They may receive care-coordination assistance in obtaining preventive and therapeutic oral health care for mother and newborn/infant.
- Newborn/infant participants will receive oral health interventions, fluoride varnish up to four times and oral health care referral where indicated.
- CHRs will receive training in oral health assessment for adults and infants. They will also be trained in Motivational Interviewing (MI) techniques which are recommended for pediatric dental care.[5]

The MI content will begin with existing materials developed for other AI/AN projects (e.g., American Indian and Alaska Native Motivational Interviewing Guide developed by Dr. Kamilla Venner and modified for the prevention of ECC[10]). The ECC behavioral risk factors listed below will be emphasized, along with the 5 main principles that govern MI

sessions: 1) the expression of empathy; 2) the development of discrepancy between what is and what is desired; 3) the avoidance of argumentation; 4) rolling with resistance; and 5) support for self-efficacy. MI was identified as a culturally resonant technique to employ in this study because previous literature suggests that MI communication strategies are congruent with AI values and practices.[11]

Each MI session will follow this general outline: 1) introduction of the specific subject of the session, relating this to community educational and promotional materials; 2) exploration of the pros and cons of change in the specific area; 3) assessment of the importance of change to the participant and confidence of the participant in their ability to make the change; 4) enhancement of the participant's self-efficacy through identification of what they think they will be able to accomplish; 5) elicitation of commitment language to follow through on the decision reached in the session; and 6) development of a follow-up plan, with specific action steps. The MI manual has been developed in an iterative process using the CAB's at each site.

CHRs will be AI lay persons, with a high school education or higher, selected from within the AI communities. Two CHRs will be hired at each site, one to implement the OH intervention and the other to implement the HL comparison intervention. CHRs implementing the OH intervention will complete didactic and clinical education including basics of OH care.

The OH educational intervention consists of six 1-hour sessions covering the following topics/modules: maternal oral health, take your child to the dentist, clean infant's mouth/brush child's teeth two times a day, limit sweets/offer non-sugar foods and drinks, offer only plain water in bottles or sippy cups in bed, and germs cause cavities/reduce germ sharing. The first session (baseline) will cover maternal oral health and the remaining five sessions will be selected by the mothers per topic on the agenda setting worksheet within the MI framework. All sessions will utilize MI dialogue, visuals, some hands-on activities or skill-building practice, and hand-outs summarizing the topics covered. Sessions will occur at approximately 4 and 7 months prenatal, and 6, 12, 18, and 24-27 months postnatal. At Visit 2, mothers will receive OH homecare supplies (toothbrush and toothpaste) for themselves. At Visits 3, 4 and 6 mothers will receive toothbrush and toothpaste for their baby.

CHRs will guide mothers through agenda and goal setting for each topic by asking questions about what their goals are for baby's teeth, what is important to them, what concerns/worries they have about baby's oral health, what makes them want to change ways of caring for their child's teeth, why it is important, and what makes them feel a need for change. Mothers will rate the importance of their goals and their level of confidence in achieving them. Consistent with MI processes, the CHRs will encourage commitment language, assist mothers in developing a change plan, and distribute take home sheets.

Maternal Oral Health Module

This is presented at the first session in the 4-month prenatal period and focuses on maternal oral healthcare needs/going to the dentist, oral-systemic connection, preventing germ-sharing, daily brushing and flossing/oral care, modeling good behaviors, and fresh food is best/best foods for oral health. Details of the oral health intervention are in the Manual of Operations.

Healthy Lifestyle Intervention

The behavioral intervention for participants in the healthy lifestyle comparison group will include a standard prenatal/postnatal education curriculum which includes educational material from the National Head Start curriculum. The goal is to educate women on topics such as nutrition and diet, physical activity, breastfeeding/formula feeding, substance use, mental/emotional health, infant/child care and development milestones. Details of the healthy lifestyle intervention are in the Manual of Operations. Parallel to the OH arm, at Visit 2 mothers will receive adult toothbrush and toothpaste for themselves and at Visits 3, 4 and 6 mothers will receive toothbrush and toothpaste for their baby.

6.7 Administration of Intervention

The interventions will be delivered by the trained CHRs. There are 6 one-hour sessions for each treatment arm, two prepartum and four postpartum. The CHRs will be scheduled to meet with study participants in their homes and, whenever possible, the same CHR will meet with the same study participants for each of the study sessions.

6.8 Procedures for Training Interventionists and Monitoring Intervention Fidelity

All research team members from both Montana and Arizona (including CHRs) will attend a 2-day training in Flagstaff, Arizona. All will be trained on the research protocol, consent process, and data collection methods. Oral health and motivational interviewing specialists will train the OH CHRs in motivational interviewing techniques, including practicing MI skills. The OH CHRs training will encompass ECC detection, fluoride varnish application, and oral health education skills. Another set of team members will train the HL CHRs in delivering the HL comparison intervention based on the standard Head Start curriculum.

After the two days of initial training, each of the CHRs will be scheduled to have follow-up calls with the trainers to clarify any further questions they might have. Initial calibration of CHRs with study participants will be done by continued monitoring of MI sessions through audio recording, transcription, and review. CHRs will receive immediate feedback. To ensure consistent intervention delivery at each site, CHR adherence and competence will be monitored throughout the study period. During bimonthly site visits team staff will meet with the site PIs and coordinators to review any difficulties and brainstorm responses to site-specific challenges. NAU and Tribal research team members will conduct follow-up trainings on a monthly basis for the first

6 months of the intervention and telephone coaching thereafter. CHRs delivering the Healthy Lifestyle intervention will also provide feedback regarding difficulties and site-specific challenges. MI trainings and fidelity monitoring will be recorded in a MI Training and Fidelity log.

A manual of instructions for conducting the MI intervention will be developed. The MI CHRs will be thoroughly trained on conducting the MI intervention, and this training will be reinforced annually. The study investigators will be present at all training sessions. The MI CHRs will also be able to refer to the manual of instructions on a daily basis for reinforcement.

The on-site project coordinators for the study will observe each MI CHR on a monthly basis to make sure that the MI intervention is being competently performed at the field level. The study investigators at NAU will review the data collected at the home MI visits as described above.

During the study, all MI sessions will be audio recorded using the hand-held recorders which are then uploaded onto encrypted laptop computers to be saved on the secure data server. NAU staff will review a random sample of 20% of the intervention recordings, scoring them against the MITI criteria (Motivational Interviewing Treatment Integrity Scale, available through the University of New Mexico Center for Center on Alcoholism, Substance Abuse, and Addiction[12]). Details of the scoring criteria are in the MOP. Adequate MI proficiency will be based on meeting or exceeding each of the following criteria: covering an average of 3.5 out of 5 global score dimensions (Evocation, Collaboration, Autonomy/Support, Direction, and Empathy); maintaining a 1:1 question to reflection ratio; asking 50% of questions in an open vs. closed manner; 90% or higher MI adherent statements. CHRs will be given immediate feedback for each of the audited intervention sessions as to their adherence and competence in the use of MI. CHRs will be asked to participate in self-reflection on their adherence and competence as part of the supervision and feedback sessions.

We will make every effort to retain CHRs for the entire duration of the data collection phase of the study. However, if a CHR leaves, our lead MI trainer will be asked to train a new CHR and after training, calibration will be done in a manner identical to the first CHRs.

6.9 Assessment of Participant Compliance with Study Intervention

CHRs for both the Oral Health intervention and the Healthy Lifestyle intervention will keep detailed records on their encounter forms for each visit with each family, including the date of the visit, term of pregnancy or age of the child, what content was selected for discussion (oral health group only), their satisfaction with the visit, dental aids left with the family (oral health group only) and other members of the family participating. CHRs will also keep track of all missed visits, including the number of attempts to schedule each visit through use of a password protected call log. Missed attendance within the pre-specified visit window (see Study Schedule Section 7) will be considered a protocol violation. Missed appointments within the visit window will be recorded but are not protocol violations.

7 STUDY SCHEDULE

7.1 Screening

Project staff will collaborate with LBHC and the CAB at Crow and the WIC clinic and Head Start staff at Hopi to identify pregnant women who meet inclusion criteria. Written information explaining the study purpose will be disseminated to all potential participants. Participants will be given an orientation to the project, including the intervention schedule and study risks and benefits. No medical record screening is required for participation.

Screening Visit (Day -28 to -1)

Confirm that potential participants are:

- 18 years or older
- Pregnant (3-7 months)
- American Indian or giving birth to an AI child (as reported by the mother)
- Able and willing to participate until the child is age 3
- Living within approximately 100 miles of the Crow or Hopi Nations
- Not enrolled in other community health interventions that incorporate oral health intervention, e.g., Family Spirit Program at Hopi
- Not a member of the Northern Cheyenne Tribe
- Not living on the Navajo Nation and a not a member of the Navajo Tribe

Following confirmation of eligibility participants may be consented into the study. At this point the formal coverage of the consent form will occur and study staff will obtain and document consent from potential participants. Following completion of informed consent (documented in REDCap) the participant will be randomized by NAU staff to either the Healthy Lifestyle or Oral Health arm. At this point participants are officially enrolled in the study and will be referred to a CHR to schedule the first study visit. A small subset of demographic questions (~20 items) will be assessed at the consent visit.

7.2 Visit 1 Overview/Baseline

Baseline data will be collected on the mothers/caregivers, including oral health knowledge and attitudes; social support, insurance and health care utilization. Mothers/caregivers in the OH group will receive the first MI intervention module. Mothers in the HL group will receive the first Healthy Lifestyle intervention module.

7.3 Study Visit Descriptions

7.3.1 Visit 1 (3-7 months pregnant; 9-31 weeks pregnant)

The range of months is broad because of the potential difficulty of enrolling expectant mothers at a precise gestational epoch. We will make every effort to recruit women shortly after the first trimester but to facilitate enrollment women through 7 months of pregnancy are eligible which will still permit a second intervention session at least 30 days after the first session and prior to giving birth.

- Obtain sociodemographic assessments; oral health knowledge and attitudes; oral health self-efficacy; maternal and child health knowledge.
- Administer the OH or HL intervention.

7.3.2 Visit 2 (7-9 months pregnant; 28-40 weeks)

- Visit 2 must occur at least 30 days after visit 1.
- Administer the OH or HL intervention.
- Assess social determinants such as transportation, health literacy, dentist trust, social relationship resources.
- Record participant's compliance with OH or HL intervention.
- Record adverse events as reported by participant or observed by investigator.

7.3.3 Visit 3 (Child 6 months of age ± 1 month)

- Assess child demographics, insurance and transportation; social determinants; communication, trust and satisfaction with CHR.
- Administer the OH or HL intervention.
- Administer fluoride varnish to any erupted teeth among OH arm children.
- Record participant's compliance with OH or HL intervention.
- Record adverse events as reported by participant or observed by investigator.

7.3.4 Visit 4 (Child 12 months of age ± 1 month)

- Visit 4 may take place over two days. The child's oral health assessment and FV application will always go first (i.e., on Day 1) and the OH/HL intervention will follow (on Day 2). These may be completed on the same day as long as the oral assessment and FV application happen first.
- Child oral health assessment for both OH and HL arms.
- Administer fluoride varnish to erupted teeth among OH and HL arm children.

- Assess oral health knowledge, behavior and attitudes; maternal/child health knowledge; social determinants; dental self-efficacy, trust and satisfaction with CHR; social support.
- Administer the OH or HL intervention.
- Record participant's compliance with OH or HL intervention.
- Record adverse events as reported by participant or observed by investigator.

7.3.5 Visit 5 (Child 18 months of age ± 2 months)

- Assess oral health locus of control, health literacy, social integration, financial stability, transportation health care utilization, trust and satisfaction with CHR.
- Administer the OH or HL intervention.
- Record number of erupted teeth in children in OH and HL groups.
- Administer fluoride varnish to erupted teeth among OH arm children.
- Record participant's compliance with OH or HL intervention.
- Record adverse events as reported by participant or observed by investigator.

7.3.6 Visit 6 (Child 24 months of age ± 2 months)

- Visit 6 may take place over two days. The child's oral health assessment and FV application will always go first (i.e., on Day 1) and the OH/HL intervention will follow (on Day 2). These may be completed on the same day as long as the oral assessment and FV application happen first.
- Child oral health assessment for both OH and HL arms.
- Administer fluoride varnish to erupted teeth among OH and HL children. This will be the **final visit** for late cohort participants.
- Obtain psychosocial assessments; oral health knowledge and behavior; oral health self-efficacy; maternal and child health knowledge, attitudes towards oral health; child oral health quality of life; insurance and health care utilization; trust and satisfaction with CHR. Record number of erupted teeth in each treatment group.
- Administer the OH or HL intervention.
- Record participant's compliance with OH or HL intervention.
- Record adverse events as reported by participant or observed by investigator.

7.4 Final Study Visit 7 (Child 30-36 months of age [early cohort only])

- Child oral health assessment for both OH and HL arms.
- Administer fluoride varnish to erupted teeth among OH and HL arm children (early enrollees only; this will be their **final visit**).

- Record number of erupted teeth in children in each arm.
- Record participant's compliance with OH or HL intervention.

7.5 Withdrawal Visit

If a mother/caregiver/child drops out of the study early and refuses additional follow-up, an early termination visit will be requested. If this request is accepted, a dmfs measure for the child will be obtained along with a questionnaire to the mother/caregiver about sociodemographic factors; dental knowledge, attitudes, and behavior; psychological influences; other health and risk factors; other dental interventions received; and the reasons for early termination. If the early termination visit is refused, we will ask if they are willing to continue to be followed without the intervention. If the participant wishes to fully withdraw we will withdraw them and their child from the study.

7.6 Unscheduled Visit

If an unscheduled visit is done, the home visit data will be collected, including reason for visit, date of visit, age of child, content of visit, mother/caregivers decisions regarding next steps, mother/caregiver's satisfaction with visit, and other family members participating.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Study Procedures/Evaluations

All children in the study will have an oral assessment at ages 12 and 24 months with approximately half of children followed until 30-36 months with a third oral assessment. Oral assessments will include dmfs evaluation. Procedures for the oral assessments will be defined by the Caries Outcome Work Group of the ECC consortium. The criteria for the determination of dmfs measures will be according to Drury, et al.[13] These criteria include the counting of cavitated caries lesions. Dmft scores for the secondary outcome will be derived from dmfs scores. The number of teeth with decayed surfaces will be divided by the number of erupted teeth to create the dmft score. If no teeth have been filled or are missing due to disease this will be dt rather than dmft.

8.1.1 Survey Assessments

We will use surveys to assess the remaining secondary outcomes as well as other social and community resources and barriers related to health. The secondary outcomes include oral health knowledge, oral health behavior, attitudes towards oral health care and maternal/child health knowledge. These are described in Section 3.2. Other domains include social determinants of health (e.g., insurance, transportation; physical living conditions; social support), and trust and satisfaction with the CHR. Specific survey items and scoring are in the MOP.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Safety parameters will include all serious adverse events (SAEs) experienced by participants in this study. Unanticipated problems (UPs) occurring in the research will also be reported as per IRB requirements.

9.1.1 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.

9.1.2 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.

9.1.3 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.

9.2 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 for those completing the full study period and who agree to be recontacted. At each study visit, the CHR will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

9.3 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.

9.3.1 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.

9.3.2 Expectedness

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

9.3.3 Severity of Event

The following scale will be used to grade adverse events:

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

9.4 Reporting Procedures

9.4.1 Unanticipated Problem Reporting

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 **10 business days** (as per NAU guidelines; https://nau.edu/wp-content/uploads/sites/74/2018/05/Reporting-Local-Information_v2019.8.pdf) of the investigator becoming aware of the event. Any other unanticipated problem will be reported to the IRB within **10 business days** of the investigator becoming aware of the problem
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the 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 Medical Monitor 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

9.4.2 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

The study's clinically responsible individual will complete a Serious Adverse Event Form and submit via fax or email within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the Serious Adverse Event Form and submitted to Product Safety within **1 day** (*as per NAU IRB requirements*) of site awareness.
- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported by fax within 10 days of site awareness.

All SAEs will be followed until resolution or stabilization.

9.4.3 Reporting of Safety Events to FDA

Not applicable

9.4.4 Events of Special Interest

Not applicable.

9.4.5 Reporting of Pregnancy

Not applicable.

9.5 Halting Rules

The frequency of UPs or SAEs in this study is expected to be very small. If the number of SAEs is unexpectedly large, or of a particular type, NIDCR and the DSMB may consider temporarily suspending enrollment to the study and the study intervention 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.

10 STUDY OVERSIGHT

In addition to the PI's responsibility for oversight, study oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) appointed by the NIDCR. The DSMB will operate under the rules of an NIDCR-approved charter that will be approved at the organizational meeting of the DSMB. The conduct of the DSMB and rules regarding how often the Board will meet will be defined by the DSMB charter for the study. At this time, most data elements that the DSMB needs to assess will be clearly defined. It is anticipated that the DSMB will meet at least once per year via teleconference to assess safety and efficacy data, study progress, and data integrity for the study. If safety concerns arise, more frequent meetings may be held. The DSMB will operate under the rules of an NIDCR-approved charter that will be approved at the organizational meeting of the DSMB. At this time, most data elements that the DSMB needs to assess will be clearly defined. The DSMB will provide recommendations to the NIDCR.

11 CLINICAL SITE MONITORING

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the NIDCR's Clinical Research Operations and Management Support (CROMS) contractor. The monitor will evaluate study processes and documentation based on the International Council for Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP).

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP). The CMP will specify the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Staff from CROMS will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the CMP. Documentation of monitoring activities and findings will be provided to the site study team, the study PIs, NIDCR-OCTOM, and NIDCR Program staff. The NIDCR reserves the right to conduct independent clinical site monitoring as necessary.

12 STATISTICAL CONSIDERATIONS

12.1 Study Hypotheses

This study examines the effect of a bundled "best practices" intervention that includes locally tailored dietary and oral health education provided during pregnancy and the postnatal period; 2) oral health care of children including the application of fluoride varnish; 3) motivational interviewing with children's mothers; and 4) patient navigation of existing oral health and other social services in each study community, facilitated by CHRs. This treatment will be compared to a healthy lifestyle intervention which includes maternal and child health, child developmental milestones, nutrition and other healthy behavior.

Primary outcome

Number of decayed, missing or filled primary tooth surfaces – dmfs – at the last oral assessment
The hypothesis for the primary outcome dmfs is that a bundled "best practices" oral health and fluoride varnish intervention will reduce early childhood caries relative to a healthy lifestyle intervention comparison group.
Ho: mean oral health group dmfs = mean healthy lifestyle group dmfs
Ha: mean oral health group dmfs $\neq$ mean healthy lifestyle group dmfs

If this hypothesis is confirmed we will then calculate the prevented fraction which "…is the difference in mean caries increments between the treatment and control groups expressed as a percentage of the mean increment in the control group" (Marinho et al. 2013, p. 1). This will be a descriptive supplement to the primary endpoint analysis rather than a separate statistical hypothesis test. We do not plan to analyze twelve month dmfs data but will incorporate 12 month assessments in models to multiply impute missing dmfs scores for the last assessment.

Secondary endpoints

Average number of decayed, missing or filled teeth at the last oral assessment (dmft; excluding non-cavitated lesions)
Hypothesis: average dmft will be lower in the oral health group
Ho: oral health group average dmft = healthy lifestyle group average dmft
Ha: oral health group average dmft $\neq$ healthy lifestyle group average dmft

Mother/caregiver oral health knowledge at Visit 6
Hypothesis: caregiver oral health knowledge will be higher in the oral health group
Ho: mean oral health group oral health knowledge = mean healthy lifestyle group oral health knowledge
Ha: mean oral health group oral health knowledge $\neq$ mean healthy lifestyle group oral health knowledge

Mother/caregiver oral health behavior at Visit 6
Hypothesis: caregiver oral health behavior will be higher in the oral health group
Ho: mean oral health group oral health behavior = mean healthy lifestyle group oral health behavior
Ha: mean oral health group oral health behavior ≠ mean healthy lifestyle group oral health behavior

Caregiver attitudes towards oral health care at Visit 6
Hypothesis: caregiver oral health attitudes will be higher in the oral health group
Ho: mean oral health group attitudes = mean healthy group lifestyle attitudes
Ha: mean oral health group attitudes ≠ mean healthy lifestyle group attitudes

Maternal/child health knowledge at Visit 6
Hypothesis: caregiver maternal/child health knowledge will be higher in healthy lifestyle group
Ho: mean oral health group maternal/child knowledge = mean healthy lifestyle group maternal/child knowledge
Ha: mean oral health group maternal/child knowledge ≠ mean healthy lifestyle group maternal/child knowledge

12.2 Sample Size Considerations

A Cochrane meta-analytic review[9] estimated that fluoride varnish reduces the prevalence of decayed, missing and filled first teeth surfaces (dmfs) by 37%. An Indian Health Services survey reported a mean dmfs in 2-year olds of 10.05 (standard deviation [SD]=16.27).[14] A 37% reduction from this low base rate would require prohibitively large samples from these communities. To increase sensitivity and efficiency we will follow our sample from a minimum of 2 years and some children to a maximum of 3 years of age. Recent data from 3-year olds on the Navajo Nation showed a mean dmfs of 18.2 (SD=19.4). Therefore, for sample size calculations, we estimate values halfway between ages 2 and 3, i.e., mean dmfs=14 (SD=17.25). Using Stata 15.1 (StataCorp, College Station, TX) with power = 0.80, alpha = 0.05 (two tailed) for an independent *t*-test a sample of 352 is necessary to detect a 37% reduction in caries experience (dmfs of 14 vs 8.8; SD=17.25). To cover the estimated 19% attrition rate reported in the Cochrane review would require 434 participants. This is the theoretical maximum sample size necessary in this context. However, sample size estimates are highly sensitive to the estimated variability of dmfs measurements. A 35% reduction in the standard deviation (SD=11.2) for the same effect size would require only 150 participants for power = 0.80 (N=185 to cover attrition). Prior studies in AI groups have not evaluated fluoride varnish application in combination with prenatal maternal intervention using MI techniques and care coordination. This novel and intensive treatment combination should produce a larger effect than varnish alone and also reduce extreme caries experience, i.e., reduce dmfs variability. Our statistical sensitivity is also enhanced by following early enrollees up to an average expected age of ~ 2.5 years. Our recruitment timeline targets enrollment of 350 pregnant women across both sites. With 19% attrition we would retain an effective sample size of 283.5. To be

conservative we round down to an even number of 282 (141 per group) which provides power of 0.71 for a 2-tailed test with alpha .05 and a 37% treatment group difference in dmfs. This sample size achieves power = 0.97 under the smaller standard deviation assumption. Current standards of care recommend FV application for all children at high risk for caries. Study staff will therefore apply FV to children in the Healthy Lifestyle group at 12 and 24 months of age. This will potentially dilute between groups caries differences but is a necessary accommodation given the high caries burden in AI communities.

We feel this is a statistically defensible target enrollment given the high fluoride varnish application frequency in our study and the ~ 2.5 years of follow-up time from birth. Moreover, genuine treatment effects occurring below our statistical detection threshold or within highly variable decay experiences are unlikely to be clinically and ecologically relevant. Both calculations are based upon the average effects of fluoride varnish alone[9] and thus should be conservative. In this regard an Australian trial that enrolled expectant Aboriginal women suggests the combination of MI and fluoride varnish results in a larger treatment effect than varnish alone[3] and that this difference persisted over 5 years of follow up.[15] Power analysis based upon their data is presented in the section below.

On average 9 and 23 women per month give birth at Hopi and Crow, respectively. We target recruiting 7 per month at Hopi and 18 per month at Crow. This will achieve our target enrollment by 14 months and will accrue a larger number of participants at Crow (N=252) than Hopi (N=98). Our study is not designed to compare intervention effectiveness across tribes but rather across treatment groups. Therefore, the enrollment imbalance across sites does not affect our primary research question as both groups will be combined when evaluating all outcomes.

Secondary outcome power analysis

Secondary outcomes include a complementary caries measure and a set of caregiver-assessed health knowledge and behavior domains.

Average number of teeth with decay. The secondary oral health outcome measure is the average number of decayed, missing or filled teeth (dmft) as defined by cavitated lesions (or worse). We count only cavitated lesions because this threshold is used in other AI studies[1,2] and because of low examiner reliability for identifying noncavitated lesions.[16] Treatment with three fluoride varnish applications and motivational interviewing produced an average difference of –0.19 teeth with cavitated lesions (95% CI –0.23, –0.16) among 2-year old children.[3] Because the variability of this measure is substantially lower (SD=0.22), statistical power to detect this treatment difference with 100 per group using an independent *t*-test exceeds 0.99 with alpha = 0.05 two-tailed. Doubling this variability estimate (SD=0.44) provides power of 0.86 with 100 per group. Another approach is to calculate power using the lower 95% confidence limit for the treatment group difference in Jameison et al. That difference estimate (–0.16) provides power > 0.99 with 100 per group. If no missing or filled teeth are observed (as was the case in Jamieson) we will analyze the outcome as dt.

Oral health knowledge. With a sample size of 282 this study has power of 0.81 to detect a 15% difference in post-test knowledge scores across the treatment groups (e.g., 65% vs. 80% correct).

12.3 Planned Interim Analyses (if applicable)

There are no planned interim analyses for the primary or secondary outcomes. We will provide summary statistics of social health determinants (insurance, transportation, social relationship resources) and health behavior (tobacco and alcohol use) to each Tribal community based upon the baseline assessment only. This will be returned after we complete our last enrollee (expected in month 14 of recruitment).

12.4 Final Analysis Plan

Descriptive analyses will include calculating means and proportions and their associated measures of variability. We will also compare key sociodemographic differences across those who do and do not complete the study (attrition analysis). As per CONSORT guidelines[17] we will not statistically compare participant baseline characteristics across treatment arms.

Missing data. We will multiply impute missing values for the primary outcome for all participants enrolled and randomly assigned to a treatment (intention to treat). We will impute within each treatment group[18] based upon key sociodemographic factors (maternal age and education; tribe; child sex) assuming the data are missing at random. Multiply imputed estimates of regression coefficients and standard errors will be combined using Rubin's rules. The primary outcome is a continuous variable.

The focal intention to treat analysis of the intervention will be evaluated by regressing dmfs at follow up on a binary treatment group variable using robust variance estimates. We will include child sex, child age in months at follow up and site (Hopi/Crow) as covariates. Although randomization should balance the treatment groups, age and sex are strongly associated with dmfs scores[7] and covarying those variables should increase efficiency. Covarying child age also statistically controls for follow up length. In contrast, covarying the (log) number of tooth surfaces in analysis of childhood caries did not predict dmfs in a similar RCT.[2] We are not powered to compare treatment differences across site but using site as a covariate will increase sensitivity in the context of possible site differences in caries.

Robust variance estimation in OLS regression will provide more accurate variance estimates in the presence of assumptive violation, i.e., heteroscedasticity. If the model is homoscedastic robust regression will provide estimates close to non-robust OLS estimates.[19] This approach obviates the need to prespecify the correct form of assumptive violation.

Analysis of the oral health secondary outcome (dmft) will parallel dmfs analyses. Other secondary outcomes involving questionnaires will regress post-test scores (Visit 6) on a binary treatment indicator variable using baseline values as a covariate.

Should we observe treatment effects on caries we will conduct exploratory analysis of possible mediators including oral health knowledge, behavior, efficacy, and structural barriers such as transportation.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of 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.

Source documents will include both paper and electronic data forms. Paper data forms include informed consent forms, encounter forms, and SAE and UP report forms. Electronic data forms include sociodemographic and oral health survey data, dental assessment data, and IHS dental and health records. Consent forms will be kept in locked file cabinets, separate from all other participant records. Identifying information such as name, address, and phone number will be maintained on each mother or caregiver/child in the study for the purposes of recontact and follow-up. This information will be kept in locked file cabinets in the study field offices.

The web-based Clinical Trials Management Software (CTMS) system REDCap will be the original source for scheduled and actual study visits; questionnaire data; adverse event reports, and protocol deviations. Data from other sources (dental assessment data) will be uploaded into REDCap. These data will be kept on a secure password-protected server (ADAMS) accessible only to project staff.

Whenever possible, data will be entered directly into an iPad. Based on available data, the rate of possible system failure is estimated at <1%. In the eventuality of a system outage or internet service failure, back-up paper forms for data capture and subsequent system entry are available.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The PI has the ultimate responsibility for implementing and maintaining quality assurance and quality control systems with written operating procedures to ensure that the trial is conducted and data are generated, documented and reported in compliance with the protocol. The Fidelity Monitoring Coordinator and Data Collection Coordinator will provide regular reports on the fidelity and administration of the intervention to the PI.

The study team leadership will 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.

The PI and key personnel will 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 the overall intervention program.

The Data Collection Coordinator will serve as the Quality Management Coordinator and will utilize clinical trials monitoring systems available through REDCap, NIDCR and study documents to monitor quality control of all study activities. This will include the documentation and maintenance of records, and generation of regular reports for both internal (within study team) and quarterly and/or annual reports, as scheduled, to the NIDCR. These will provide the status of study preparation (including CHR trainings, dental examiner trainings and calibration sessions and results) and study activities (including participant recruitment, activities completion including intervention deliveries by sites, incentives dispersal, and data (withdrawals) and safety (AE, SAE) monitoring). All of these major activities will utilize checklists to ensure and document completion of procedures. (More details can be found in the Data Management Plan and the Quality Management Plan).

A. Recruitment and tracking. NAU staff and CHRs at Hopi and Crow will be trained on procedures and scripts, will use eligibility checklists, and will document study eligibility. Participant personal identifying information will be maintained in a secure location (REDCap) to allow tracking across study activities.

B. Consent procedures. Informed consent will be obtained by Site Coordinators at Hopi and Crow. Participants will complete paper consents, and consents will be collected and stored in locked files. Documentation of informed consent will be maintained in REDCap.

C. Assessment completion. All study staff will be trained to complete data collection processes. All staff trainings will be documented as to activity and date completed. Assessment completion will be overseen and recorded by date in REDCap. 1) CHRs will be trained to administer questionnaires using mobile devices via REDCap 2) The

dental assesor will conduct the oral assessment and the CHR will enter dental assessment data into REDCap.

D. Intervention training, delivery, and fidelity monitoring. Study interventions will be delivered by CHR facilitators who are trained by study investigators/personnel and evaluated for fidelity to the intervention plan. Training binders and toolboxes will be utilized to increase standardization and fidelity. All trainings will be documented. New CHRs will receive the same training. All intervention sessions will be documented and audiotaped for fidelity monitoring purposes. Facilitators will receive feedback to address any issues identified in the fidelity evaluation.

E. Examiner training and calibration. Persons performing the oral assessments will attend trainings and calibration sessions conducted by our oral health training team. We will model calibration procedures found in Warren et al.[16] These are described in the MOP.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

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

15.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the NAU, Phoenix Area IHS and the Rocky Mountain Tribal IRBs for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRBs before the changes are implemented in the study.

15.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and benefits of participation in the study will be provided to the mothers/caregivers and their families. Consent forms describing in detail the healthy lifestyle and the MI intervention, study duration and procedures, and risks and benefits will be given to the mothers, and written documentation of informed consent will be required prior to starting the study.

All adult participants will be required to sign a written consent form before participating in the study. Verbal consent will not be accepted. A form with contact information for the study PI and Project Coordinators will be provided to each participant. Participants will be given an orientation to the project, including intervention schedule, study risks and benefits, and compensation information. All participants will have adequate time to ask questions or request more information

Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with others or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants 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.

Consent forms will be required for the calibration participants and expectant mother participants, who also consent for their babies in their original baseline consent forms. Re-consent is necessary only in the event of a protocol change.

The consent process will be documented in REDCap.

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

The proposed clinical trial participants will include pregnant women and eventually their newborn infants. Participants must be a tribal member (as defined by the mother) or be giving birth to an AI child. Males are not excluded, but a male would only be enrolled should the study child have a change in caregiver. In that case we would seek informed consent of the new primary caregiver and enroll that caregiver in the study.

15.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the study sponsor(s) and their agents. This confidentiality is extended to cover all clinical information, sociodemographic data, and data on psychosocial measures and dental knowledge, attitudes, and behaviors.

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

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

Research records will be handled as confidentially as possible. All study data used for research purposes will contain only a study ID and have names, addresses, and other information removed for data analysis so they cannot be identified by name. Paper study records will be kept in locked files available only to those persons requiring access for research purposes. No individual identities will be used in any reports or publications resulting from the Healthy Smiles trial.

Subject PHI, including contact information, and study visit windows and actual dates will be stored in a tracking database residing on NAU’s secure servers accessible only to study staff.

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

N/A

16 DATA HANDLING AND RECORD KEEPING

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

16.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the Principal Investigator. All source documents must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

Staff will utilize a secure web-based data-entry system (REDCap, Forte Research Systems) to input questionnaire and clinical data and to monitor study participant status. Each staff person will have a unique login ID with strong passwords and access and permissions restricted to data consistent with their given roles within the study. Each participant will be assigned a unique study ID number to be used on each electronic case report form for identification and tracking purposes.

Systems and procedures will comply with HIPAA. In addition to unique IDs for each staff member, passwords will be required to have a specific length and combination of alphanumeric and special characters to mitigate social hacking of passwords. Users are required to register for access to the ADAMS server at NAU and accept strict conditions for handling and analyzing the data. ADAMS is a remote desktop server that is available for researchers to store and analyze what “high risk data.” High risk data may be considered any data set that contains personally identifiable information, personal health information, or anything controlled by an IRB. The ability to use the server is governed and restricted by the registration process. ADAMS storage is internally backed up on the server.

16.2 Data Capture Methods

Questionnaires will be self-administered in English directly into REDCap using cellular-enabled tablets which will upload responses directly to the secure NAU server. In the absence of cellular service responses may be acquired and stored offline within the REDCap environment on the tablet and uploaded later. CHRs will also carry hard copy surveys as backup in case of catastrophic tablet failure. Dental assessment results will be directly entered into a REDCap database via a custom graphical interface. Access to REDCap is password protected and study staff will be authorized to access data acquisition areas limited to their site and study responsibilities.

16.3 Types of Data

Data stored in paper format include the consent forms and the HIPAA documents and other intervention forms. Electronic data will include sociodemographic data; dental knowledge, attitudes, and behaviors; other psychosocial data; MI visit data; dental utilization data; and data from the children's oral health assessment. Study administrative data, such as contact information, data collection windows, and intervention appointments will also be maintained electronically. A separate REDCap shell will house safety data.

16.4 Schedule and Content of Reports

Periodic reports documenting study progress will be generated by REDCap and reviewed by the PI and co-investigators at monthly meetings. These reports include: (i) a tabular enrollment report that summarizes enrollment progress, number of participants who completed the study protocol, number of participants who discontinued early; (ii) a listing of each subject deviation and protocol deviation with dates, descriptions, and actions taken; (iii) a listing of participant study activities (e.g., questionnaire, dental assessment) that were completed and missed; (iv) a report with graphical and tabular summaries of cumulative (versus planned) accrual and follow-up visit attendance; dental assessment visit completion.

Aggregated annual reports will be submitted to the DSMB.

16.5 Study Records Retention

Study records will be maintained for at least three years from the date that the last grant federal financial report (FFR) is submitted to the NIH (https://grants.nih.gov/grants/policy/nihgps/html5/section_8/8.4.2_record_retention_and_access.htm).

All study records and computer files will be retained for at least 3 years after the final study manuscript is published. All paper study records will be destroyed 3 years after IRB acknowledgement of study closure in accordance with HIPAA regulations. Electronic study records will be destroyed after the 3 year window according to Tribal agreements.

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.

Protocol deviations, unplanned deviations from expected protocol that are unintended, will include study events that are missed (interventions not delivered, delivered at a different time point than scheduled, or not received), and assessments and dental assessments conducted outside of the expected protocol windows. Deviations will be recorded and monitored in REDCap and reported to the NIDCR, NAU and IHS IRBs,

and the DSMB, according to their requirements. 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 in ICH E6.

17 PUBLICATION/DATA SHARING

This study will comply with all applicable NIH Data Sharing Policies. These policies may be modified by Tribal agreements.

This study will comply with the NIH *Public Access Policy* which 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.

Following completion of the study, the investigators will prepare manuscripts of the results to be submitted to peer-reviewed scientific journals for publication.

As with all NIDCR-supported research, all materials submitted for publication, publications and reports resulting from activities supported by this award will acknowledge support from the National Institute of Dental and Craniofacial Research, NIH, specifically referencing the grant number. An acknowledgment shall be made to the effect that:

“The project was supported by Award Number 1U01DE028508-01 from the National Institute of Dental & Craniofacial Research. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Dental & Craniofacial Research or the National Institutes of Health.”

As requested by the REDCap team, we will also acknowledge NIH grant support provided to the REDCap development team for that data acquisition system (UL1 TR000445 from NCATS/NIH).

“REDCap is supported in part by NIH/NCATS UL1 TR000445”

Authorship

Investigators will decide on authorship of scientific documents prior to writing them. The principles set forth in the ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals (the “Vancouver Rules”) will be followed and/or the authorship rules of the specific journals.

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 summary results of these trials are submitted to ClinicalTrials.gov. A “responsible party” (i.e., the principal investigator or designee) will register the trial before recruitment begins and report summary results of the clinical trial at the end of the study.

18 LITERATURE REFERENCES

1. Braun PA, Quissell DO, Henderson WG, et al. A cluster-randomized, community-based, tribally delivered oral health promotion trial in Navajo Head Start children. *J Dent Res.* 2016;95(11):1237-1244.
2. Batliner TS, Tiwari T, Henderson WG, et al. Randomized trial of motivational interviewing to prevent early childhood caries in American Indian children. *JDR Clin Trans Res.* 2018;3(4):366-375.
3. Jamieson L, Smithers L, Hedges J, et al. Dental disease outcomes following a 2-year oral health promotion program for Australian aboriginal children and their families: a 2-arm parallel, single-blind, randomised controlled trial. *EClinicalMedicine.* 2018;1:43-50.
4. Phipps KR, Ricks TL. The oral health of American Indian and Alaska Native children aged 1-5 years: results of the 2014 IHS oral health survey. *Indian Health Service Data Brief.* 2015. https://www.ihs.gov/doh/documents/IHS_Data_Brief_1-5_Year-Old.pdf. Accessed 14 July 2019.
5. Review Council American Academy of Pediatric Dentistry. Behavior guidance for the pediatric dental patient. *Pediatr Dent.* 2017;40(6):254-267.
6. Garcia RI, Gregorich SE, Ramos-Gomez F, et al. Absence of fluoride varnish-related adverse events in caries prevention trials in young children, United States. *Prev Chronic Dis.* 2017;14:E17.
7. Tiwari T, Quissell DO, Henderson WG, et al. Factors associated with oral health status in American Indian children. *J Racial Ethn Health Disparities.* 2014;1(3):148-156.
8. Batliner T, Fehringer KA, Tiwari T, et al. Motivational interviewing with American Indian mothers to prevent early childhood caries: study design and methodology of a randomized control trial. *Trials.* 2014;15:125.
9. Marinho VC, Worthington HV, Walsh T, Clarkson JE. Fluoride varnishes for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev.* 2013(7):CD002279.
10. Venner K, Feldstein SW, Tafoya N. Native American Motivational Interviewing: weaving Native American and western practices; A manual for counselors in Native American communities. 2006. https://www.samhsa.gov/sites/default/files/programs_campaigns/samhsa_hrsa/native-american-motivational-interviewing.pdf. Accessed 14 July 2019.
11. Albino JEN, Orlando VA. Promising directions for caries prevention with American Indian and Alaska Native children. *Int Dent J.* 2010;60(3S2):216-222.
12. Moyers TB, Martin T, Manuel JK, Miller WR, Ernst D. Revised Global Scales: Motivational Interviewing Treatment Integrity 3.1.1 (MITI 3.1.1). In. Center on Alcoholism, Substance Abuse and Addictions (CASAA): University of New Mexico; 2010.
13. Drury TF, Horowitz AM, Ismail AI, Maertens MP, Rozier RG, Selwitz RH. Diagnosing and reporting early childhood caries for research purposes: A report of a workshop sponsored by the National Institute of Dental and Craniofacial

Research, the Health Resources and Services Administration, and the Health Care Financing Administration. *J Public Health Dent.* 1999;59(3):192-197.

14. Indian Health Service. An oral health survey of American Indian and Alaska Native dental patients: findings, regional differences and national comparisons. ND. *http://dhss.alaska.gov/dph/wcfh/Documents/oralhealth/docs/Oral_Health_1999_IHS_Survey.pdf*. Accessed 15 July 2019.
15. Jamieson L, Smithers L, Hedges J, et al. Follow-up of intervention to prevent dental caries among indigenous children in Australia: A secondary analysis of a randomized clinical trial. *JAMA Network Open.* 2019;2(11):e1915611-e1915611.
16. Warren JJ, Weber-Gasparoni K, Tinanoff N, et al. Examination criteria and calibration procedures for prevention trials of the Early Childhood Caries Collaborating Centers. *J Public Health Dent.* 2015;75(4):317-326.
17. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol.* 2010;63(8):e1-37.
18. Bell ML, Fairclough DL. Practical and statistical issues in missing data for longitudinal patient-reported outcomes. *Stat Methods Med Res.* 2014;23(5):440-459.
19. Stata Corporation. Hetregress — heteroskedastic linear regression. In: *Stata base reference manual, release 15.* College Station, TX: Stata Press; 2017:1075.

SUPPLEMENTAL MATERIALS

Dental assessment calibration protocol

Data and Safety Monitoring Board charter

Manual of Procedures

APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

Procedures	Gestation in months				Child age in months					
	Screening/enrollment (3-7 months)	**Visit 1** (3-7 months)	**Visit 2** (7-9 months)	Birth of child	**Visit 3*** (6 months ± 1)	**Visit 4** (12 months ± 1)	**Visit 5** (18 months ± 2)	**Visit 6** (24 months ± 2; ½ cohort)	**Visit 7** (30-36 months ± 2; ½ cohort)	Premature Discontinuation
Assessment of eligibility criteria	X									
Signed consent form	X									
Demographics	X				X					
Oral Health Intervention		X	X		X	X	X	X		
Fluoride varnish - Oral Health arm					X	X	X	X	X (**early cohort**)	[X]
Healthy Lifestyle Intervention		X	X		X	X	X	X		
Fluoride Varnish – Healthy Lifestyle arm						X		X (**late cohort**)	X (**early cohort**)	[X]
Oral assessment (dmfs)						X		X (**late cohort**)	X (**early cohort**)	[X]
Assessment of adverse events			X		X	X	X	X	X	[X]
Oral health behavior						X		X		
Oral health attitudes		X				X		X		
Oral health knowledge		X				X		X		
Maternal/child health knowledge		X				X		X		
Social determinants (e.g., insurance, transportation)		X			X		X			
Social determinants (social relationship resources)			X			X	X	X		
Social determinants (dental care provider trust, satisfaction)			X			X	X	X		
Community health representative communication, trust, satisfaction					X	X	X	X		[X]
Pediatric health related quality of life								X		

*****Postnatal study treatments are based upon child age not gestation period. Therefore times for Visits 3-7 are based upon child age. Cells with [X] denotes observation or treatment provided conditional on premature discontinuation.

APPENDIX B: Fluoride Varnish Regulatory Data Sheet

Regulatory Data Sheet

This Regulatory Data Sheet is provided as a courtesy in response to a customer request.

Document Group:	26-9856-1	Version Number:	5.00
Issue Date:	06/25/18	Supercedes Date:	08/07/17

12149/12150/12151/12154/12159/12160 3M™ ESPE™ VANISH™ 5% NaF WHITE VARNISH WITH TCP

3M
Oral Care Solutions Division
3M Center, St. Paul, MN 55144-1000, USA
1-888-3M HELPS (1-888-364-3577)

RDSs are available at www.3M.com

Regulations and Industry Standards

SDS (US OSHA)
See Safety Data Sheet (SDS) for hazard and other regulatory data.

US FALCPA
This product complies with the United States Food Allergy Labeling and Consumer Protection Act of 2004, as there is no intentionally added milk, egg, fish, crustacean shellfish, tree nuts, wheat, peanuts, soybeans, and/or proteins thereof.

EU CMR Directive
This product contains an ingredient at >= 0.1% that is classified as a Category 1 or 2 carcinogen, mutagen, or reproductive toxicant according to Annex VI (Table 3.2) of European Regulation 1272/2008 on Classification, Labelling, and Packaging of Dangerous Substances and Mixtures or that is classified by 3M or its vendors as an EU Category 1 or 2 carcinogen, mutagen, or reproductive toxicant according to the criteria of European Council Directive 67/548/EEC (the Dangerous Substances Directive).

EU Food Allergens
This product complies with Regulation (EU) 1169/2011 on the provision of food information to consumers, as there is no intentionally added component identified in Annex II of this regulation. Specifically, none of the following are intentionally added: cereals containing gluten, crustaceans, eggs, fish, peanuts, soybeans, milk, nuts, celery, mustard, sesame seeds, sulphur dioxide and sulphites at concentrations of more than 10 mg/kg or 10 mg/L expressed as sulphur dioxide, lupin, mollusks, and/or derivatives thereof.

Halal
This product has not been certified Halal.

Kosher
This product has not been certified Kosher.

California Proposition 65

This product contains a chemical/chemicals that have been recognized by the State of California to cause cancer or reproductive harm.

Chemicals and/or Compounds of Interest

Arsenic and (As) Compounds : This chemical or chemical compound is not intentionally added.
Beryllium and (Be) Compounds : This chemical or chemical compound is not intentionally added.
Bismuth and (Bi) Compounds : This chemical or chemical compound is not intentionally added.
Bisphenol A (BPA) : This chemical or chemical compound is not intentionally added.
Butyl Benzyl Phthalate (BBP) : This chemical or chemical compound is not intentionally added.
Cadmium and (Cd) Compounds : This chemical or chemical compound is not intentionally added.
Chromium and (Cr) Compounds : This chemical or chemical compound is not intentionally added.
Colophony (Rosin) : This product is known to contain this chemical or chemical compound. *An inactive ingredient of this product is "Pentaerythritol Glycerol Ester of Colophony Resin" which is a modification of the naturally occurring rosin (colophony) derived from pine tree sap. For more information on this, please contact the 3M Customer Care Center at 1-800-634-2249.*
Dibutyl Phthalate (DBP) : This chemical or chemical compound is not intentionally added.
Dibutyl Tin Compounds : This chemical or chemical compound is not intentionally added.
Di(2-Ethylhexyl) Phthalate (DEHP) : This chemical or chemical compound is not intentionally added.
Diisodecyl Phthalate (DIDP) : This chemical or chemical compound is not intentionally added.
Diisononyl Phthalate (DINP) : This chemical or chemical compound is not intentionally added.
Di-n-Octyl Phthalate (DNOP) : This chemical or chemical compound is not intentionally added.
Dyes : This chemical or chemical compound is not intentionally added.
Flavorings : This product is known to contain this chemical or chemical compound.
Formaldehyde : This chemical or chemical compound is not intentionally added.
Gluten : This chemical or chemical compound is not intentionally added.
Hexavalent Chromium and (Cr+6) Compounds : This chemical or chemical compound is not intentionally added.
Lead and (Pb) Compounds : This chemical or chemical compound is not intentionally added.
Melamine : This chemical or chemical compound is not intentionally added.
Mercury and (Hg) Compounds : This chemical or chemical compound is not intentionally added.
Natural Rubber Latex : This product is not made with natural rubber latex.
Nickel and (Ni) Compounds : This chemical or chemical compound is not intentionally added.
Nuts : This chemical or chemical compound is not intentionally added.
Organotin Compounds : This chemical or chemical compound is not intentionally added.
Phthalates : This chemical or chemical compound is not intentionally added.
Selenium and (Se) Compounds : This chemical or chemical compound is not intentionally added.
Tributyl Tin Compounds : This chemical or chemical compound is not intentionally added.
Triphenyl Tin Compounds : This chemical or chemical compound is not intentionally added.
Zinc and (Zn) Compounds : This chemical or chemical compound is not intentionally added.

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APPENDIX C: Fluoride Varnish Material Safety Data Sheet

MATERIAL SAFETY DATA SHEET 12149/ 12150/ 12151/ 12154 3M™ ESPE™ VANISH™ 5% NaF WHITE VARNISH WITH TCP 06/12/12

Material Safety Data Sheet

SECTION 1: PRODUCT AND COMPANY IDENTIFICATION

PRODUCT NAME: 12149/ 12150/ 12151/ 12154 3M™ ESPE™ VANISH™ 5% NaF WHITE VARNISH WITH TCP
MANUFACTURER: 3M
DIVISION: 3M ESPE Dental Products

ADDRESS: 3M Center, St. Paul, MN 55144-1000

EMERGENCY PHONE: 1-800-364-3577 or (651) 737-6501 (24 hours)

Issue Date: 06/12/12
Supercedes Date: 04/28/10

Document Group: 26-9856-1

Product Use:

Intended Use:	Dental Product
Limitations on Use:	For use only by dental professionals
Specific Use:	Fluoride Varnish

SECTION 2: INGREDIENTS

Ingredient	C.A.S. No.	% by Wt
PENTAERYTHRITOL GLYCEROL ESTER OF COLOPHONY RESIN	Not available	30 - 75
n-HEXANE	110-54-3	10 - 15
ETHYL ALCOHOL	64-17-5	1 - 15
SODIUM FLUORIDE	7681-49-4	1 - 5
FLAVOR ENHANCER	Not available	1 - 5
THICKENER	Not available	1 - 5
FOOD GRADE FLAVOR	Not available	1 - 5
MODIFIED TRICALCIUM PHOSPHATE	Not available	< 5

SECTION 3: HAZARDS IDENTIFICATION

3.1 EMERGENCY OVERVIEW

Specific Physical Form: Liquid

Odor, Color, Grade: Light yellow liquid with mint, cherry or melon odor
General Physical Form: Liquid
Immediate health, physical, and environmental hazards: Flammable liquid and vapor. Closed containers exposed to heat from fire may build pressure and explode. This document has been prepared in accordance with the U.S. OSHA Hazard Communication Standard, which requires the inclusion of all known hazards of the product or ingredients regardless of the potential risk. The risks of the hazards communicated in this document may vary depending on the potential for exposure. See Section 3.2 for other hazards that can be associated with the ingredients in this product in a non-emergency situation.

3.2 POTENTIAL HEALTH EFFECTS

Eye Contact:
Moderate Eye Irritation: Signs/symptoms may include redness, swelling, pain, tearing, and blurred or hazy vision.

Skin Contact:
Moderate Skin Irritation: Signs/symptoms may include localized redness, swelling, itching, and dryness.

Inhalation:
Respiratory Tract Irritation: Signs/symptoms may include cough, sneezing, nasal discharge, headache, hoarseness, and nose and throat pain.

Prolonged or repeated exposure may cause:
Respiratory Effects: Signs/symptoms may include cough, shortness of breath, chest tightness, wheezing, increased heart rate, bluish colored skin (cyanosis), sputum production, changes in lung function tests, and/or respiratory failure.

May be absorbed following inhalation and cause target organ effects.

Ingestion:
May be harmful if swallowed.

Gastrointestinal Irritation: Signs/symptoms may include abdominal pain, stomach upset, nausea, vomiting and diarrhea.

Chemical (Aspiration) Pneumonitis: Signs/symptoms may include coughing, gasping, choking, burning of the mouth, difficulty breathing, bluish colored skin (cyanosis), and may be fatal.

May be absorbed following ingestion and cause target organ effects.

Target Organ Effects:
Central Nervous System (CNS) Depression: Signs/symptoms may include headache, dizziness, drowsiness, incoordination, nausea, slowed reaction time, slurred speech, giddiness, and unconsciousness.

Prolonged or repeated exposure may cause:
Liver Effects: Signs/symptoms may include loss of appetite, weight loss, fatigue, weakness, abdominal tenderness and jaundice.

Kidney/Bladder Effects: Signs/symptoms may include changes in urine production, abdominal or lower back pain, increased protein in urine, increased blood urea nitrogen (BUN), blood in urine, and painful urination.

Neurological Effects: Signs/symptoms may include personality changes, lack of coordination, sensory loss, tingling or numbness of the extremities, weakness, tremors, and/or changes in blood pressure and heart rate.

Peripheral Neuropathy: Signs/symptoms may include tingling or numbness of the extremities, incoordination, weakness of the hands and feet, tremors and muscle atrophy.

Hard Tissue Effects: Signs/symptoms may include color changes in the teeth and nails; changes in development of bone, teeth or nails; weakening of the bones; and/or hair loss.

MATERIAL SAFETY DATA SHEET 12149/ 12150/ 12151/ 12154 3M™ ESPE™ VANISH™ 5% NaF WHITE VARNISH WITH TCP 06/12/12

Contains a chemical or chemicals which can cause birth defects or other reproductive harm.
NOTE: This product contains ethanol. There are data associating human consumption of alcoholic beverages (ethanol) with developmental toxicity. This is not an expected effect during the foreseeable use of this product.

Carcinogenicity:
Contains a chemical or chemicals which can cause cancer.

NOTE: This product contains ethanol. Alcoholic beverages and ethanol in alcoholic beverages have been classified as human carcinogens by the International Agency for Research on Cancer, the U.S. National Toxicology Program, and the California Environmental Protection Agency (for purposes of Proposition 65). Exposure to ethanol during the foreseeable use of this product is not expected to cause cancer.

Ingredient	C.A.S. No.	Class Description	Regulation
ETHYL ALCOHOL	64-17-5	Grp. 1: Carcinogenic to humans	International Agency for Research on Cancer

SECTION 4: FIRST AID MEASURES

4.1 FIRST AID PROCEDURES

The following first aid recommendations are based on an assumption that appropriate personal and industrial hygiene practices are followed.

Eye Contact: Flush eyes with large amounts of water. If signs/symptoms persist, get medical attention.
Skin Contact: Remove contaminated clothing and shoes. Immediately flush skin with large amounts of water. Get medical attention. Wash contaminated clothing and clean shoes before reuse.
Inhalation: Remove person to fresh air. If signs/symptoms develop, get medical attention.
If Swallowed: Do not induce vomiting. Give victim two glasses of water. Never give anything by mouth to an unconscious person. Get immediate medical attention.

SECTION 5: FIRE FIGHTING MEASURES

5.1 FLAMMABLE PROPERTIES

Autoignition temperature	*No Data Available*
Flash Point	25 ºC [*Test Method:* Closed Cup]
Flammable Limits(LEL)	*No Data Available*
Flammable Limits(UEL)	*No Data Available*

5.2 EXTINGUISHING MEDIA
Use fire extinguishers with class B extinguishing agents (e.g., dry chemical, carbon dioxide).

5.3 PROTECTION OF FIRE FIGHTERS

Special Fire Fighting Procedures: Water may not effectively extinguish fire; however, it should be used to keep fire-exposed containers and surfaces cool and prevent explosive rupture. Wear full protective equipment (Bunker Gear) and a self-contained breathing apparatus (SCBA).

Unusual Fire and Explosion Hazards: Flammable liquid and vapor. Closed containers exposed to heat from fire may build pressure and explode.

Note: See STABILITY AND REACTIVITY (SECTION 10) for hazardous combustion and thermal decomposition information.

SECTION 6: ACCIDENTAL RELEASE MEASURES

6.1. Personal precautions, protective equipment and emergency procedures
Evacuate unprotected and untrained personnel from hazard area. The spill should be cleaned up by qualified personnel. Cover, but do not seal for 48 hours.

6.2. Environmental precautions
For larger spills, cover drains and build dikes to prevent entry into sewer systems or bodies of water. Place in a metal container approved for use in transportation by appropriate authorities. The container must be lined with polyethylene plastic or contain a plastic drum liner made of polyethylene.

Clean-up methods
Observe precautions from other sections. Call 3M- HELPS line (1-800-364-3577) for more information on handling and managing the spill.

In the event of a release of this material, the user should determine if the release qualifies as reportable according to local, state, and federal regulations.

SECTION 7: HANDLING AND STORAGE

7.1 HANDLING
Keep away from heat, sparks, open flame, pilot lights and other sources of ignition. Avoid breathing of vapors, mists or spray. Use general dilution ventilation and/or local exhaust ventilation to control airborne exposures to below Occupational Exposure Limits. If ventilation is not adequate, use respiratory protection equipment. Avoid eye contact. Avoid prolonged or repeated skin contact. Wash hands after handling and before eating.

7.2 STORAGE
Store away from acids. Store away from heat. Store away from oxidizing agents. Store in a cool, dry place.

SECTION 8: EXPOSURE CONTROLS/PERSONAL PROTECTION

8.1 ENGINEERING CONTROLS
Use with appropriate local exhaust ventilation. Use in a well-ventilated area.

8.2 PERSONAL PROTECTIVE EQUIPMENT (PPE)

8.2.1 Eye/Face Protection
Avoid eye contact.
The following eye protection(s) are recommended: Safety Glasses with side shields
.

8.2.2 Skin Protection
Avoid prolonged or repeated skin contact. Gloves not normally required.

8.2.3 Respiratory Protection
Under normal use conditions, airborne exposures are not expected to be significant enough to require respiratory protection. Avoid

breathing of vapors, mists or spray.

8.2.4 Prevention of Swallowing
Do not ingest. Wash hands after handling and before eating.

8.3 EXPOSURE GUIDELINES

Ingredient	Authority	Type	Limit	Additional Information
ETHYL ALCOHOL	ACGIH	STEL	1000 ppm	
ETHYL ALCOHOL	OSHA	TWA	1900 mg/m3	
FLUORIDES	ACGIH	TWA, as F	2.5 mg/m3	
FLUORIDES	OSHA	TWA, as dust	2.5 mg/m3	
FLUORIDES	OSHA	TWA, as F	2.5 mg/m3	
Hexane	ACGIH	TWA	50 ppm	Skin Notation*
Hexane	OSHA	TWA	1800 mg/m3	
n-HEXANE	ACGIH	TWA	50 ppm	Skin Notation*
n-HEXANE	OSHA	TWA	1800 mg/m3	

* Substance(s) refer to the potential contribution to the overall exposure by the cutaneous route including mucous membrane and eye, either by airborne or, more particularly, by direct contact with the substance. Vehicles can alter skin absorption.

SOURCE OF EXPOSURE LIMIT DATA:
ACGIH: American Conference of Governmental Industrial Hygienists
CMRG: Chemical Manufacturer Recommended Guideline
OSHA: Occupational Safety and Health Administration
AIHA: American Industrial Hygiene Association Workplace Environmental Exposure Level (WEEL)

SECTION 9: PHYSICAL AND CHEMICAL PROPERTIES

Specific Physical Form:	Liquid
Odor, Color, Grade:	Light yellow liquid with mint, cherry or melon odor
General Physical Form:	Liquid
Autoignition temperature	*No Data Available*
Flash Point	25 ºC [*Test Method:* Closed Cup]
Flammable Limits(LEL)	*No Data Available*
Flammable Limits(UEL)	*No Data Available*
Boiling Point	68 ºC
Density	0.8 g/ml
Vapor Density	*Not Applicable*
Vapor Pressure	*Not Applicable*
Specific Gravity	0.8 [*Ref Std:* WATER=1]
pH	*Not Applicable*
Melting point	*Not Applicable*
Solubility in Water	Moderate
Evaporation rate	*Not Applicable*
Kow - Oct/Water partition coef	*Not Applicable*
Viscosity	*No Data Available*

SECTION 10: STABILITY AND REACTIVITY

Stability: Stable.

Materials and Conditions to Avoid:
10.1 Conditions to avoid
Heat

10.2 Materials to avoid
Strong oxidizing agents
Strong acids

Hazardous Polymerization: Hazardous polymerization will not occur.

Hazardous Decomposition or By-Products

Substance	Condition
Carbon monoxide	During Combustion
Carbon dioxide	During Combustion

SECTION 11: TOXICOLOGICAL INFORMATION

Please contact the address listed on the first page of the MSDS for Toxicological Information on this material and/or its components.

SECTION 12: ECOLOGICAL INFORMATION

ECOTOXICOLOGICAL INFORMATION

Not determined.

CHEMICAL FATE INFORMATION

Not determined.

SECTION 13: DISPOSAL CONSIDERATIONS

Waste Disposal Method: Incinerate uncured product in a permitted hazardous waste incinerator.
As a disposal alternative, dispose of waste product in a permitted hazardous waste facility.

EPA Hazardous Waste Number (RCRA): D001 (Ignitable)

Since regulations vary, consult applicable regulations or authorities before disposal.

SECTION 14:TRANSPORT INFORMATION

ID Number(s):
70-2010-5739-8, 70-2010-5740-6, 70-2010-5741-4, 70-2010-5742-2, 70-2010-5743-0, 70-2010-5744-8, 70-2010-5745-5, 70-2010-5746-3, 70-2010-5747-1, 70-2010-5748-9, 70-2010-5749-7, 70-2010-5750-5, 70-2010-5751-3, 70-2010-5752-1, 70-2010-8812-0, 70-

2010-8813-8, 70-2010-8814-6, 70-2010-8815-3, 70-2010-8816-1, 70-2010-8817-9, 70-2010-8818-7, 70-2010-8819-5, 70-2010-8820-3, 70-2010-8821-1, 70-2010-8822-9, 70-2010-8823-7, 70-2010-8824-5, 70-2010-8825-2, 70-2010-8826-0, 70-2010-8838-5, 70-2010-8839-3, 70-2010-8840-1, 70-2010-8849-2, 70-2010-8850-0, 70-2010-8851-8

For Transport Information, please visit http://3M.com/Transportinfo or call 1-800-364-3577 or 651-737-6501.

SECTION 15: REGULATORY INFORMATION

US FEDERAL REGULATIONS
Contact 3M for more information.

311/312 Hazard Categories:
Fire Hazard - Yes Pressure Hazard - No Reactivity Hazard - No Immediate Hazard - Yes Delayed Hazard - Yes

Section 313 Toxic Chemicals subject to the reporting requirements of that section and 40 CFR part 372 (EPCRA):

Ingredient	C.A.S. No	% by Wt
n-HEXANE	110-54-3	10 - 15
n-HEXANE (Hexane)	110-54-3	10 - 15

STATE REGULATIONS
Contact 3M for more information.

CHEMICAL INVENTORIES
This material contains one or more substances not listed on the TSCA Inventory. Commercial use of this material is regulated by the FDA.

Contact 3M for more information.

INTERNATIONAL REGULATIONS
Contact 3M for more information.

This MSDS has been prepared to meet the U.S. OSHA Hazard Communication Standard, 29 CFR 1910.1200.

SECTION 16: OTHER INFORMATION

NFPA Hazard Classification
Health: 2 **Flammability:** 3 **Reactivity:** 0 **Special Hazards:** None

National Fire Protection Association (NFPA) hazard ratings are designed for use by emergency response personnel to address the hazards that are presented by short-term, acute exposure to a material under conditions of fire, spill, or similar emergencies. Hazard ratings are primarily based on the inherent physical and toxic properties of the material but also include the toxic properties of combustion or decomposition products that are known to be generated in significant quantities.

Reason for Reissue: Change in MSDS ingredient disclosure.

Revision Changes:
Section 1: Product use information was modified.
Section 16: Disclaimer (second paragraph) was modified.
Section 10: Hazardous decomposition or by-products table was modified.
Section 3: Carcinogenicity phrase was modified.
Section 14: Transportation legal text was modified.

Section 9: Density information was modified.
Section 9: Boiling point information was modified.
Section 5: Flammable limits (UE) information was modified.
Section 5: Flammable limits (LEL) information was modified.
Section 5: Autoignition temperature information was modified.
Section 9: Vapor density text was modified.
Section 9: Vapor pressure text was modified.
Section 5: Flash point information was modified.
Sections 3 and 9: Odor, color, grade information was modified.
Section 9: Property description for optional properties was modified.
Section 9: Specific gravity information was modified.
Section 9: pH information was modified.
Section 9: Melting point information was modified.
Section 9: Solubility in water text was modified.
Section 9: Flash point information was modified.
Section 9: Flammable limits (LEL) information was modified.
Section 9: Flammable limits (UEL) information was modified.
Section 9: Autoignition temperature information was modified.
Section 14: ID Number(s) Template 1 was modified.
Section 2: Ingredient table was modified.
Section 15: EPCRA 313 information was modified.
Section 8: Exposure guidelines ingredient information was modified.
Section 3: Carcinogenicity table was modified.
Section 6: 6.2. Environmental precautions heading was added.
Section 6: 6.1. Personal precautions, protective equipment and emergency procedures heading was added.
Section 16: Web address was added.
Section 1: Address was added.
Copyright was added.
Company logo was added.
Section 6: Clean-up methods heading was added.
Telephone header was added.
Company Telephone was added.
Section 1: Emergency phone information was added.
Section 1: Emergency phone information was deleted.
Company Logo was deleted.
Copyright was deleted.
Section 16: Web address heading was deleted.
Section 6: Release measures heading was deleted.
Section 1: Address line 1 was deleted.
Section 1: Address line 2 was deleted.

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MATERIAL SAFETY DATA SHEET 12149/ 12150/ 12151/ 12154 3M™ ESPE™ VANISH™ 5% NaF WHITE VARNISH WITH TCP 06/12/12

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