CenteringPregnancy Oral Health Promotion (CPOP) Clinical Trial

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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 (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

SIGNATURE PAGE

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

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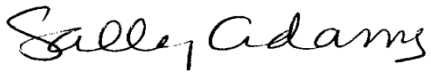
Signed:  Date: October 14, 2020

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ASTDD	Association of State and Territorial Dental Directors
BOP	Bleeding on Probing
BSS	Basic Screening Survey
CAN DO	Center to Address Disparities in Children's Oral Health
CC	Coordinating Center
CFR	Code of Federal Regulations
CFU	Colony Forming Units
CP	CenteringPregnancy®
CPOP	CenteringPregnancy® Oral Health Promotion
CRA	Clinical Research Associate
CRF	Case Report Form
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLMM	Generalized Linear Mixed Model
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
KAB	Knowledge, Attitudes and Behaviors
LB	Lactobacillus
MS	Mutans Streptococci
N	Number (typically refers to subjects)
NIDCR	National Institute of Dental and Craniofacial Research, NIH, DHHS
NIH	National Institutes of Health
OCTOM	Office of Clinical Trials Operations and Management, NIDCR, NIH
OH	Oral Health
OHRP	Office for Human Research Protections
PD4	Probing Depth >4mm
PI	Principal Investigator

PLI	Plaque Index
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
TVC	Total Viable Count
UP	Unanticipated Problem
US	United States

PROTOCOL SUMMARY

Title:

CenteringPregnancy Oral Health Promotion (CPOP) Clinical Trial

Précis:

A five-year, Phase III, multi-site, cluster randomized controlled clinical trial will evaluate the efficacy of the CenteringPregnancy (CP) Oral Health Promotion (CPOP) intervention. Intervention and control groups will be drawn from 5 CP sites. Prenatal care facilitators will conduct the intervention in group prenatal care sessions. With 2-5 CP facilitators per site (14 facilitators), conducting 3-4 CP groups each (49 CP groups with 8 mother/child dyads per group), the total study population will be approximately 392 mother-child dyads. CP facilitators will be randomly assigned to either the: 1) intervention arm and deliver the CPOP intervention; or 2) control arm and deliver the usual CP curriculum. The CPOP intervention consists of two 15-minute modules: 1) maternal oral health (OH) and 2) infant OH. The data collection will continue through 12 months postpartum. For the maternal OH module, pre- and post-intervention dental exams of gingival OH and Plaque Levels, and knowledge, attitudes and behavior (KAB) questionnaires during the prenatal period will be used to assess maternal OH outcomes. For the infant OH module, pre and post-module KAB questionnaires will be completed during the prenatal period. Infant OH risk status – the presence of caries-causing bacteria *(*mutans streptococci and *Lactobacilli)* in saliva of both mother and infant will be assessed when the infant is 12 months of age to determine differences in study arms.

Analyses will include generalized linear mixed model regressions testing a treatment by time interaction to determine the significance of differences between intervention arms from pre-to post- intervention on the outcome variables. Additional analyses (Secondary Aim 2) will test mediation effects of knowledge, attitudes, and behaviors on relationships between treatment arm and primary study outcomes.

Objectives:

Primary Aim 1: Determine if women in CP groups that include the CPOP intervention as part of their CP prenatal care will have significantly greater improvement in clinical OH and hygiene outcomes during pregnancy (reduced % sites with bleeding on probing (BOP), reduced % sites with probing depths ≥4mm (PD4), and reduced Plaque Index scores) compared to women receiving CP usual care.

Primary Aim 2: Determine if infants of mothers in CP groups that include the CPOP intervention as part of their CP prenatal care will be significantly less likely to have the presence of caries-causing salivary

bacteria (mutans streptococci) at 12 months of age, compared to infants of mothers receiving CP usual care.

Secondary Aim 1: Determine if women in CP groups that include the CPOP intervention as part of their CP prenatal care, compared to women receiving CP usual care will have significantly greater increases in:

- Maternal OH knowledge, attitudes, and hygiene behaviors during pregnancy;
- Maternal infant-related OH knowledge and attitudes during pregnancy and at 12 months postpartum; and
- Maternal OH practices with their infant at 12 months postpartum.

Secondary Aim 2: Determine if infants of mothers in the CPOP intervention groups are significantly less likely to have the presence of caries-causing salivary bacteria (*Lactobacilli*) at 12 months of age, compared to infants of mothers receiving CP usual care.

Secondary Aim 3: Determine if maternal OH knowledge, attitudes, and/ or behaviors mediate the relationships between intervention arm and maternal OH and infant OH risk (salivary bacteria incidence) outcomes.

Population: 392 healthy mother-infant dyads coming from a broad range of socio-demographic backgrounds. Women receiving their prenatal care in CenteringPregnancy® group prenatal care programs will be enrolled into the CPOP study from the 2nd through prior to the 3rd of their 10 scheduled CP sessions. CP group care is available at clinics and hospitals in the San Francisco Bay Area. CPOP participants will be involved in the study from their study enrollment during pregnancy through 12 months postpartum. Women will participate during their pregnancies within their prenatal care sessions and data collection visits to complete assessments and dental examinations. Both mothers and infants will participate at 12 months postpartum.

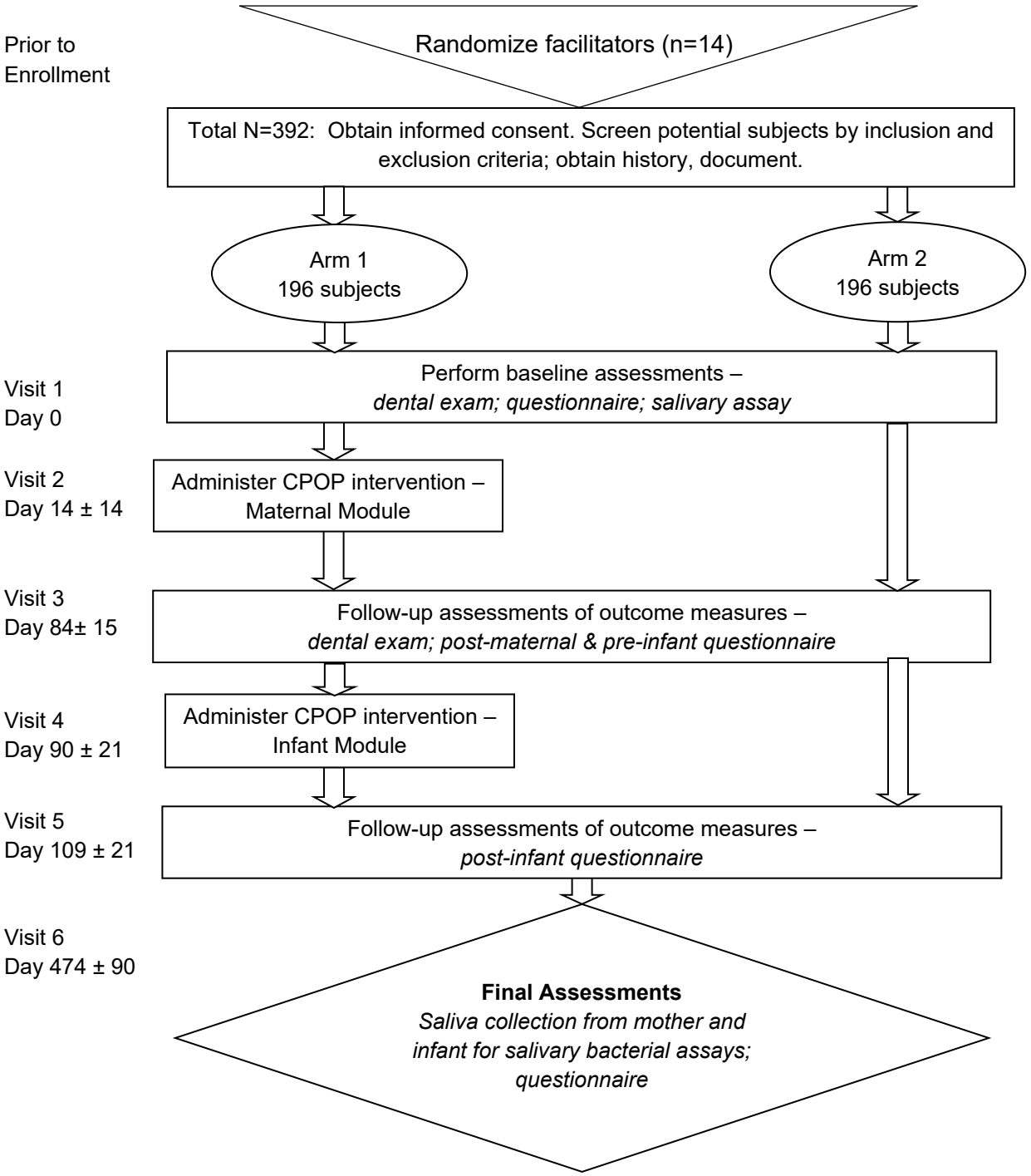
Phase: III

Number of Sites: 5 sites

Description of Intervention: The intervention consists of two 15-minute interactive modules (maternal and infant OH), integrated into 2 group prenatal care sessions. Led by trained prenatal care providers (facilitators), the maternal module includes discussion of common OH problems during pregnancy, importance of OH, importance and safety of OH care during

	pregnancy, hands-on skills-building activities of learning and practicing proper tooth brushing and self-assessment of gum health, and presentation of illustrated flossing and OH promotion guides. The infant module includes discussion of infant oral hygiene, avoiding saliva sharing, proper nutrition, and importance of a dental visit by the first birthday. Activities in both modules utilize separate tool kits including tooth brushes, fluoride toothpaste, and other supplies.
Study Duration:	5 years
Subject Participation Duration:	Approximately 18 months
Estimated Time to Complete Enrollment:	3 years

Schematic of Study Design:



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2. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Poor oral health during pregnancy for many women, low rates of oral health care utilization during pregnancy, and high rates of early childhood caries are public health problems: Rationale for developing oral health programs within prenatal care

High rates of OH problems during pregnancy. Recognized as a sizable and largely preventable public health problem, maternal OH problems are very common during pregnancy, when susceptibility to periodontal disease is heightened[1]. Up to 70% of women[2,3] develop pregnancy gingivitis, from hormonal, immunological and vascular reactions to irritants such as plaque. Though this usually subsides after childbirth, women with untreated gingivitis during pregnancy are more likely to have gingivitis after pregnancy[4]. Caries prevalence, although not widely monitored during pregnancy, is an important factor in both maternal and infant OH. Recent studies indicate high caries prevalence in underserved pregnant populations[5,6]. These findings provide strong support for the guidelines that promote dental care, both for maintenance, and restorative treatments, during pregnancy.

Low dental care rates during pregnancy. Despite high rates of perinatal OH problems, only 44% of women access dental care during pregnancy, evidence of great unmet need regarding treatment and/or education for OH problems during pregnancy that would benefit OH for mothers and infants[7]. This need is greatest within low-income populations. In California, among pregnant Medicaid enrollees, only 14% accessed dental care during pregnancy[8].

High rates of early childhood caries in young children. While there is a trend of improved OH status for most age groups including young children in the U.S., still approximately one in four 2-5 year olds has either treated or untreated caries and the caries experience rate is double that for 6 – 8 year old children. Sizable disparities remain: higher rates are present in Hispanic and non-Hispanic Black children compared to non-Hispanic White children, and in children from lower- income households compared to their peers in higher-income households[9]. Early research shows that mutans streptococci (MS) and *Lactobacillus* (LB) are the primary cariogenic bacteria in ECC[10,11] and are orally transmitted from caregiver to child[12,13]. Infants mainly acquire cariogenic bacteria from mothers through salivary transmission[10,14], and mothers with high levels (>10^5 CFU/ml) are more likely to transfer bacteria to infants[15]. Reducing vertical bacterial transmission may reduce infant risk for ECC[16-19]. Thus, reducing vertical bacterial transmission should be included in OH promotion efforts during pregnancy.

Federal agencies and national professional organizations have mounted a large effort to address these public health problems. The National Maternal and Child Health Bureau[20]

has released consensus statements and clinical guidelines on perinatal OH care during pregnancy. These evidence-based guidelines promote comprehensive strategies for both dental and non-dental clinicians with the noteworthy inclusion of prenatal care providers. Integrating OH care into perinatal care is consistent with the recommendation of the National Academy of Medicine (formerly known as the Institute of Medicine) to provide OH care in various settings utilizing a diverse and expanded array of providers[21]. Including OH in prenatal care has the potential to improve women's OH through improved preventive and restorative care and to promote children's OH through caregiver education and timely anticipatory guidance.

2.2 Rationale

Rationale for integrating maternal and infant oral health interventions into CenteringPregnancy® group prenatal care

CenteringPregnancy® (CP) is an innovative prenatal group care model that provides evidence-based state-of-the-art prenatal care to women in a group setting. It was included in the AHRQ Health Care Innovations Exchange of programs that improve quality and reduce disparities. The CP model emphasizes 3 key elements to empower women to advance their health and that of their families: 1) healthcare; 2) health education; and 3) social support. Health education topics include nutrition, physical activity, tobacco/other substances cessation, partner relationships, prenatal problems, breast feeding, infant development and care, childbirth preparation, and postpartum issues. Oral health issues receive some mention but are not consistently addressed.

CP's effectiveness for prenatal care delivery has been demonstrated in a randomized controlled trial[22], and matched cohort study[23] and is associated with lower preterm birth especially among low-income African American women, higher weights of preterm babies, and greater breast feeding compared to traditional care. CP is currently involved in a Center for Medicare & Medicaid Innovation award of $4 million to test implementation of the CP model into 15 organizations. The scope of these projects highlights the potential of CP group care to significantly improve maternal and child health. The addition of an evidence-based OH promotion intervention within CP has tremendous potential to contribute to those improvements.

CP prenatal care typically includes 10 group sessions (about 2 hours in length) that typically begin early in the second trimester of pregnancy. Sessions run for approximately 25 weeks in total. The first 4 sessions are 4 weeks apart and starting at Session 4, the remainder of the sessions are typically 2 weeks apart. CP emphasizes healthcare, health education, and community building or social support. Approximately 10 women of similar gestational phase make up each group. The women begin each session with recording their blood pressure, weight, and gestational phase and the facilitator conducts a standard prenatal assessment. Then, the women and the facilitator/s gather in a circle for a general check-in, facilitated discussion, and interactive activities addressing health topics relevant to the group's gestation phase.

While CP usual care includes mention of maternal OH as one of the discomforts of pregnancy and infant OH as part of new baby care, OH is not consistently covered in a significant manner.

This study will evaluate the ability of the CPOP intervention to improve the oral health and hygiene of women during pregnancy and to reduce the presence of caries-causing salivary bacteria in their infants at 12 months of age. Data on OH knowledge, attitudes, and practices will be collected to assess the hypothesized mechanisms of action of the intervention. While the CPOP pilot study showed significant effects of the intervention, a larger randomized trial is needed to confirm its efficacy prior to disseminating it to the larger audience of CenteringPregnancy nationwide.

2.3 Description of the CPOP intervention

In this study, the CPOP study participants are recruited starting at Session 2 of the standard CP program and the CPOP maternal OH module will be delivered in the 3rd CP session when topic areas include a focus on maternal health issues. Prior to administration of the intervention, participants will have a baseline dental examination, which will be compared to a post-intervention dental exam to assess the study's primary outcome. CPOP intervention objectives cover the following: 1) a facilitated discussion to understand the common OH problems during pregnancy, the importance of maternal OH for mothers and infants and the importance of receiving OH care during pregnancy and routinely; 2) hands-on learning and practice of proper tooth brushing and performing the Eastman Interdental Bleeding Index toothpick test of gum self-evaluation[26]; and 3) Illustrated handouts reinforcing discussion items, health practices, and instructions on proper tooth brushing and dental flossing. The Eastman toothpick test is performed by each participant at the beginning of their CP session. A toothpick is gently inserted interproximally 1-2mm at the gum line at 4 sites in their mouth, going in and out 4 times in the same spot. After a period of 15 seconds, the presence of bleeding is noted. A toolkit with OH supplies is provided for each woman. At subsequent CP sessions following the delivery of the maternal OH intervention, during the initial check in period when women check their blood pressure and weights, women also perform the Eastman toothpick test and record their results as a reinforcing activity to maintain attention on OH. CPOP pilot study results (n = 101) of the maternal OH intervention showed significant improvements in clinically assessed oral hygiene and gingival health: reduced % of gum sites that bled on probing, and reduced % of sites that were probed at ≥ 4mm depth. A slight, significant, increase was found in the intervention group for participants' ratings of the importance of OH. OH knowledge and self-efficacy did not increase significantly. Similarly, tooth brushing and dental flossing did not improve in the intervention group compared to the control group[24].

The CPOP infant OH module is delivered in the 7th or 8th CP session when CP topic areas focus more on infant factors- development and care. The CPOP infant OH module includes discussion of 5 objectives: the importance of baby teeth; avoiding saliva sharing; healthy feeding practices; cleaning and checking infant's teeth and

gums; and importance of a dental visit by age 12 months. Infant OH tool kits are provided and used as reinforcing items for the objectives. The primary outcome measure for the CPOP pilot study was salivary Mutans Streptococci (MS) prevalence in infants at 12 months of age. At 12 months, MS prevalence was significantly lower (7%) for the intervention group than for the control group (25%). At 12 months, the intervention group reported higher rates of initiating brushing their infants' teeth, and cleaning infants' gums than the control group. The groups did not differ significantly on feeding practices such as pre-tasting the infants' food on his or her spoon or ensuring the infant has his or her own spoon. The intervention group demonstrated greater increases in mothers' ratings of infant OH importance than the control group (p=0.003). Both groups reported significant increases in infant OH knowledge and the group difference was not significant.

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

CP Women: Two maternal intervention behavioral activities: 1) practicing proper tooth brushing, which is a standard recommended health behavior known to prevent dental caries; and 2) practicing the Eastman toothpick test, have no known reported risks. There is a slight risk of physical discomfort from the two dental exams. There is potentially a slight risk of discomfort in answering some of the questions about dental behaviors in the questionnaire. There is no risk to mothers providing salivary specimens for bacterial level assessments. There is a risk of a loss of confidentiality regarding participation in the study, which includes audio-recording of the intervention sessions delivered to the Intervention Arm participants.

CP 12-month old Infants: There are no risks involved with wiping a cotton swab around the gum area, nor to providing salivary specimens for bacterial assessments.

2.4.2 Potential Benefits

CP Women: Potential benefits include free dental exams for all women that include provision of basic feedback from the exam, including information about untreated decay and treatment needs. The women receiving the intervention may have increased OH knowledge, adopt favorable OH behaviors, and achieve better OH outcomes for themselves and their infants. Women receiving only the research evaluation procedures (dental examinations, salivary bacteria assessments, and questionnaires) in the control group may also adopt favorable OH behaviors which might result in better OH outcomes for themselves and their infants.

CP Facilitators: The trained CP facilitators will gain experience and confidence in delivering the OH component which may expand their own knowledge of OH and professional development, and improve their own OH behaviors and outcomes. They may also increase the quality of assistance and support they provide to pregnant women in their groups.

General benefits: It is anticipated that the information obtained in the study will help in determining the efficacy of interventions to improve maternal OH during pregnancy and prevent the development of risk factors in infants postpartum. The information may help to identify patients who may benefit the most from the intervention. And if efficacious, the CPOP intervention could become part of the standard CP curriculum and be disseminated broadly to multitudes of pregnant women across the US and any future CP programs across the world.

3. OBJECTIVES

3.1 Study Objectives

3.1.1 Primary Objective 1

Assess the efficacy of the CPOP intervention in improving maternal OH and hygiene during pregnancy. We hypothesize that women in CP groups receiving the CPOP intervention will have significantly greater improvements in their OH outcomes (comparing post-intervention dental exam to baseline) than women in the usual care CP groups: reduced % sites bleeding on probing (BOP), reduced % sites with probing depths ≥4mm (PD4), reduced Plaque Index scores.

3.1.2 Primary Objective 2

Assess the efficacy of the CPOP intervention in promoting infant OH and caries risk reduction in the first year of life. We hypothesize that infants of mothers in CP groups that include the CPOP intervention as part of their CP prenatal care will be significantly less likely to have the presence of salivary MS at age 12 months, compared to infants of mothers receiving CP usual care.

3.1.3 Secondary Objective 1

Assess the efficacy of the CPOP intervention in improving the following: 1) Maternal OH knowledge, attitudes, and hygiene behaviors during pregnancy; 2) Maternal infant-related OH knowledge and attitudes during pregnancy and at 12 months postpartum; 3) Maternal OH practices with their infant at 12 months post-partum. We hypothesize that women who receive the CPOP OH interventions will have greater increases in these three sets of indicators.

3.1.4 Secondary Objective 2

Assess the efficacy of the CPOP intervention in reducing the likelihood that infants of mothers in CP groups that include the CPOP intervention as part of their CP prenatal care will develop the presence of salivary LB at age 12 months, compared to infants of mothers receiving CP usual care.

3.1.5 Secondary Objective 3

Determine if maternal OH knowledge, attitudes, or behaviors mediate the relationships between intervention arm and maternal OH and infant OH risk (presence of salivary bacteria) outcomes. We hypothesize that the primary mechanism of action for improved maternal OH in the CPOP intervention would be improvement in oral hygiene practices (tooth brushing – change in brushing technique, frequency and/or length of time spent brushing, and flossing skills). Improvements in these practices could be due to and reinforced by increases in the following: oral hygiene skills, self-efficacy to improve and maintain good OH, OH knowledge, and perceived importance of good OH. We hypothesize that the mechanisms of action in reduction in infant oral health risk status include skills building in infant oral hygiene practices which would be promoted by increases in infant OH self-efficacy, knowledge, and importance of good infant OH.

3.2 Study Outcome Measures

3.2.1 Primary Outcomes

Outcomes for Primary Objective 1: Maternal outcomes: Clinical measures of bleeding on probing, periodontal probing depths $\geq$4mm; and plaque levels compared between the 2 intervention arms from pre- to post- intervention during pregnancy.

Outcomes for Primary Objective 2: Infant outcomes: Clinical infant measures of presence of salivary MS compared between the 2 intervention arms assessed at infant age 12 months.

3.2.2 Secondary Outcomes

Outcomes for Secondary Objective 1: Questionnaire measures of maternal OH knowledge, attitudes, and behaviors compared from pre- to post- for the 2 intervention arms; questionnaire measures of maternal knowledge and attitudes regarding infant OH promotion assessed during pregnancy and at 12 months postpartum; maternal infant care behavior differences.

Outcomes for Secondary Objective 2: Infant outcomes; clinical measures of presence of salivary LB between the 2 intervention arms at 12 months postpartum.

Outcomes for Secondary Objective 3: Mediation outcomes for maternal OH are maternal OH knowledge, attitudes (importance and self-efficacy), and behaviors (ADA-recommended tooth brushing practices and flossing). Mediation outcomes for infant OH risk are infant OH-related knowledge and attitudes (importance and self-efficacy).

4. STUDY DESIGN

Overview of Research Design. We will conduct a cluster randomized controlled clinical trial to evaluate the efficacy of the CPOP intervention within the CP prenatal care group environment. The intervention will take place during the prenatal period and participants

will be assessed pre-intervention and post-intervention while still pregnant and followed through the first year postpartum to evaluate infant and maternal outcomes.

Intervention Setting. The study will take place at 5 healthcare facilities that offer CP in the San Francisco Bay Area, most of which are community-based. The initiation of study activities in sites will be staggered in three waves approximately nine months apart, with two sites starting in each wave. CP groups at these 5 sites are conducted in either English or Spanish. We will recruit a minimum of 2-5 CP facilitators at each site to serve as either intervention or control facilitators. Facilitators will be randomized to one of two groups: 1) Intervention or 2) Control. Intervention facilitators will be trained in the intervention, which will include the facilitators practicing the Intervention delivery in a group of non-study CP moms. When study groups are initiated, the facilitators will conduct the interventions in approximately 3-4 cycles of prenatal groups. In each cycle, intervention facilitator will integrate the 2 intervention modules into 2 of their 10 CP group sessions. Control facilitators will not be trained and will not present the intervention modules within their CP groups. The control groups will receive the usual care CP curriculum. CP groups consist of 8-12 pregnant women of a similar gestational phase.

CP Facilitators. We have identified a Site Champion at each CP site, an individual with influence and connection to the clinical and administrative leadership at the health care facility. Study staff will work with these Site Champions to present an overview of the study to the facilitators and to ask them to enroll in the study. They will be assured that they are free to participate or not, however, they will be aware that their site had made a group decision to participate. The facilitators will be randomized into the Intervention or the Control arm of the study. This means that all of the pregnant women enrolled in a particular facilitator's assigned CPOP study groups will either be Intervention or Control participants.

CPOP Study Participants. Pregnant women enrolled in the CP prenatal care groups identified as study groups at each site will be invited to participate in the study. We expect that most but not all women will agree to participate in the study. However, within the Intervention CP groups, all of the women will receive the OH-integrated intervention modules (unless unenrolled women choose not to), but only enrolled study participants will complete the study questionnaire assessments and dental exams, and the salivary bacterial assays and questionnaires at 12 months postpartum. As explained above the CPOP moms will not be randomized, but rather their study group arm will be determined by their facilitator's randomly assigned place in the Intervention or the Control arm. Both Intervention and Control participants will receive OH tool kits at the time of the scheduled CPOP modules in the Intervention groups (CP session 3 for Maternal module and sessions 7 or 8 for Infant module).

CP Women participants' and CP Facilitators' data collection.

CP Women: At baseline and prior to the first (Maternal) of the two modules, participants will complete questionnaires, saliva sample collection, and a dental exam. These

activities will be scheduled for completion at the CP clinic site, outside of CP group scheduled time. A trained calibrated dental examiner will complete the dental exams in a private space, using portable dental equipment: chair, lamp, and stools. Study staff will administer the questionnaires and enter results directly into a tablet or laptop. The dental exam takes about 15-20 minutes and the questionnaires take about 15 minutes.

The Maternal Intervention Module. Intervention groups will receive the CPOP maternal intervention as part of their 3rd CP group session. Refer to Section 6.5 for details.

Approximately 10 weeks following the time of the maternal module and prior to the infant intervention module, participants complete the post-maternal module assessments consisting of a repeat dental exam and questionnaire completion. At this time, women also complete the pre-infant intervention module assessments. These consist of questionnaire assessment of infant OH knowledge and attitudes. Women receive their incentives within a week following completion of the assessments.

The Infant Intervention Module. The infant module is presented as part of the 7th or 8th CP session. Refer to Section 6.5 for details.

Approximately 2 weeks following the presentation of the Infant OH module, participants complete the post-infant OH module questionnaire assessment, repeating the earlier pre-module assessment. This may be done online with REDCap, email, or over the phone with an interview process. Women receive their incentives within a week following completion of the assessments. This is the final activity to occur during the prenatal period. Participants will receive a note from the study thanking them for their participation up to this point and reminding them that we will stay in touch with them about the study and will follow-up with them when their infants are about 10 months of age to schedule the 12-month postpartum visit.

When an infant is approximately 10 months of age, study staff will contact families to remind them of the final assessment to take place at infant age 12 months. We will assess eligibility of the infant to participate in the follow-up and confirm mother's intention to complete the final assessment. If the infant is ineligible to participate, the mother will still be eligible to complete the final assessment. The 12-month visit time will be scheduled.

The 12-month visit will occur at the participant's home or another location that is convenient for the mother and baby. Women will complete questionnaires and saliva collection procedures for assessment of salivary bacteria. The infants will complete a saliva collection procedure. Women receive their incentives within a week following completion of the assessments.

CP Facilitator participants: The CP facilitators will complete assessments of acceptability and feasibility of the CPOP Intervention at the time that study activities have come to a close in their clinics. This will include evaluation of their: satisfaction with the training and the amount of time taken to prepare for and implement the CPOP modules in their

groups; perceived value of CPOP to CP moms; perceived scalability of the interventions into the broader standard CP curriculum; and overall perceptions of the benefits versus burdens associated with the changes needed to accommodate CPOP modules in CP sessions. These data will help inform future implementation when CPOP is scaled up and disseminated broadly. These will be done online through REDCap.

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Inclusion Criteria

CP Facilitators:

- CP facilitators who conduct CP groups within the 5 designated study sites;
- ages 18 and older speak, read, and write in English;
- provide informed consent

CP Women:

- speak, read, or write in English or Spanish
- enrolled in CP prenatal group care identified as study groups
- free of any condition that requires them to take antibiotic or antibacterial medication prior to dental procedures
- provide informed consent

CP Babies:

- healthy with no acute or chronic medical conditions, especially those conditions that may have resulted in hospitalizations and subsequent exposure to pathologic microorganisms
- mothers provide informed consent for their children at baseline

Dental Exam Calibration Participants:

- ages 18 and older
- free of any condition that requires them to take antibiotic or antibacterial medication prior to dental procedures
- provide informed consent

5.2 Subject Exclusion Criteria

None

5.3 Strategies for Recruitment and Retention

CP Facilitators: Facilitators will be recruited from the 5 partner CP sites and will be randomly assigned to be either intervention or control facilitators. Facilitators will receive incentives, resources for their groups including CP notebooks, and food and beverages for the group refreshments.

CP Women receiving care in CP groups led by enrolled CPOP study facilitators: Study staff will attend the 2nd CP session and give a brief presentation describing study purpose, activities, time needed and duration of participation, incentives, options to participate, and protection of confidentiality. Women who are interested in participating can either stay after the group to get more information and/or sign informed consent, or they can give contact information and receive a follow up phone call to get more information and/or to agree to participate. The CP participant will receive reminders by text or email about their participation in the study and congratulations on their baby's birth and birthday cards. Our CP clinical sites vary in size. Estimates of women receiving CP care annually at the sites range from 53 – 176 per site (total estimated number annually who will join in CP groups led by one of the 14 study-participating CP facilitators = 340). All of our sites state that their programs are strong or robust and half of them also indicate that they are growing in size.

Calibration participants: Flyers will be posted at UCSF and other close locations to advertise the recruitment for participants. Interested adults will contact the CRA staff to get more information about the study, to determine eligibility, and receive instruction for attending the calibration session. Participants will sign consent when they arrive for the session. The CRA will send a follow up message to the participants with a reminder of the session time and date 3 days prior to the session.

5.4 Treatment Assignment Procedures

CP facilitators who are randomized to be an intervention arm facilitator will deliver the intervention to their CP participants. CP facilitators who are randomized to be a control arm facilitator will not deliver the intervention to their CP participants. Facilitators will know their assignment prior to the pregnant women in their groups being enrolled, but will be trained not to disclose this to the women.

5.4.1 Randomization Procedures

CP Facilitators will be randomly assigned to either Intervention or Control arm according to a matched, restricted randomization plan. Intervention facilitators will receive CPOP training after assignment. Our primary concern is strengthening the basis for causal inference by establishing equivalent experimental groups at baseline. Randomizing 5 sites is not optimal and randomizing CP participants is not possible because the intervention is delivered to CP groups. Therefore, we have chosen to randomize 14 CP facilitators, using "restricted randomization"[25] to ensure an acceptable level of balance across experimental groups at baseline (e.g., create two sets of CP facilitators balanced on preexisting variables describing relevant characteristics of CP sites, facilitators, and their served populations; then, randomize one set of CP facilitators to deliver CPOP and

the other to deliver usual care). Prior to randomization we will identify facilitators from our five clinical sites who agree to accept assignment as an Intervention or a Control facilitator. Once identified, we will collect descriptive data characterizing each participating CP site and facilitator, as well as the populations they serve; these data will be included in the restricted randomization process. Intervention facilitators will receive CPOP training approximately 2 months before site initiation.

Originally, we planned to randomize CP facilitators into two sets of equal size (i.e., 7 CP facilitators assigned to each set). However, with summary data in hand, preliminary restricted randomization solutions with equal set size failed to establish reasonable cross-set balance on variable describing characteristics of CP sites, facilitators, and their served populations. Next, we allowed for set sizes of with 8 and 6 CP facilitators, respectively. Allowing for an '8/6' split resulted in several restricted randomization solutions that balanced CP site, facilitator, and patient population characteristics within close tolerances. Therefore, we opted to randomize CP facilitators into two groups with one group including 8 CP facilitators and the other including 6 CP facilitators. Once a final '8/6' split was chosen, the study statistician flipped a coin to assign the two sets to CPOP Intervention versus usual care control.

5.4.2 Masking Procedures

CP Facilitators: At each CP site, CRAs will recruit the CP facilitators with the help of the CP Site Champion, specific to the CP site. Each CP Site Champion is a CP facilitator who agreed to participate in the study and to be randomized to either study arm. Training of CP Intervention facilitators at each CP site will initiate 2 months before their site is scheduled to begin recruiting patients into the study; at each CP site all CP facilitators within a CP site will be blind to random assignments until training of CP facilitators begins at their site.

CP Study Participants: Participants will complete informed consent that indicates that they may be in a CP group in which they receive additional information and activities related to their oral health and the health of their infants. They will not know whether they are in a CP group that will include the CPOP intervention until they have completed their enrollment and baseline activities. After enrollment, masking women or facilitators will not be possible. All dental examinations and salivary bacteria assays will be conducted with the evaluator masked to intervention or control arm.

5.5 Subject Withdrawal

CP Facilitators are free to withdraw from the study at any time, without penalty or loss of status at their CP clinics.

CP Participants are free to withdraw from and stop participation in the study at any time, for any reason, without penalty or loss of services at their clinics. Participants may be withdrawn for safety reasons in the case of an adverse event.

5.5.1 Reasons for Withdrawal

CP Facilitators may withdraw if they are transferred to a different CP clinic or move, if they feel that their work schedules are too demanding to remain involved in the study, or for other personal reasons.

CP women might withdraw from the study because they are moving to another location, have a miscarriage, leave the CP group care setting due to health risk reasons, decide to convert to traditional 1:1 prenatal care, or do not wish to continue in it. Women who miss the CPOP intervention module/s will be retained in the study, their attendance (yes versus no) will be recorded.

5.5.2 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

If a CP facilitator withdraws from the study, she/he will be removed from the study and another facilitator at the site will be recruited to replace her/him.

If a CP participant withdraws from the study, the study staff will document the reason and will remove them from the study. Withdrawn participants will not be replaced.

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. The previous pilot studies were categorized as minimal risk, we had high adherence to protocol requirements using the same methods, and there were no adverse events.

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 NIDCR and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

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

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

6. STUDY INTERVENTION

6.0 Adaptations to comply with UCSF requirements and guidelines for conducting research with human subjects during the COVID-19 pandemic

At this time, October 2020, we are not conducting any research activities with human subjects. We were ready to commence study activities 3 days prior to the COVID-19 pandemic coming into full focus and thus all activities were halted. Since then, we have been in regular communication with our 5 clinical study locations regarding their status of resumption of conducting prenatal care in the group setting, the timing of which has not been determined. Prior to resuming activities, we will work with the UCSF IRB, the UCSF School of Dentistry, and each clinical location's oversight leadership to determine and adhere to all safety guidelines and requirements associated with implementation and completion of our study activities. This includes conducting our facilitator training activities and the following intervention modules in our intervention groups: group discussions about oral health topics, and hands on instruction and practice of proper toothbrushing technique and learning to conduct the Eastman toothpick test, a self-assessment of gum health.

We are unable to specify details of the adaptations that we will implement at the time of study resumption because the timing of clinical resumption of group activities and the full extent of adaptations to be required is not fully known at this time. We will submit a Protocol modification addressing these to the IRB when the necessary details have been determined.

6.1 Study Behavioral or Social Intervention(s) Description

The CPOP intervention consists of two 15-minute interactive, discussion- and skills-based modules (one maternal, one infant) that fit within the CP facilitative framework. Each module utilizes a tool kit for participants containing oral hygiene supplies.

The Maternal Intervention Module:

This is presented in the 3rd CP session when the session topics focus on maternal needs and care. (See Section 2.2 for description of timing of CP Sessions.). The facilitator:

1) Introduces the topic of OH during pregnancy and distributes OH tool kits containing a toothbrush, toothpaste, and dental floss.

2) Leads an interactive discussion of: 1) common OH problems and asks women to share their experiences with these; 2) the importance of OH for the mother and the infant; and 3) the importance of receiving dental care during pregnancy and routinely afterwards. During this, the women are encouraged to discuss their opinions, beliefs and concerns about OH and OH care. The facilitator will build on

the women's basic knowledge and will direct and expand explanations as needed to clarify facts versus folk beliefs.

3) Discusses the importance of OH self-care and will lead the group in step by step tooth brushing instructions and dry brushing practice, using supplies from the tool kits. The facilitator will give feedback as needed for each woman. She will explain the rationale for learning the Eastman Interdental Assessment[26] and will instruct and guide the women to do the assessment using toothpicks and mirrors. In subsequent CP sessions, the women will conduct the toothpick test at the beginning of their sessions which is a check in time during which they monitor and record their weights and blood pressures and receive an assessment from the prenatal care provider facilitators. Women will have attended their baseline dental exams and the presence of severe periodontal issues will have been brought to their attention with the recommendation that they seek treatment as soon as possible.

4) Distributes 2 illustrated pages: 1) instructions for proper tooth brushing and flossing technique; and 2) summary review of the important elements for good OH.

The Infant Intervention Module:

The infant OH module is generally done around the 7th or 8th session when session topics focus increasingly on infant care and development. The facilitator:

1) Introduces the topic of infant OH and distributes OH tool kits containing a toothbrush, toothpaste, a small plastic- BPA-free spoon, and a small soft cloth for cleaning the inside of the infant's mouth.

2) Leads an interactive discussion of: 1) the importance of baby teeth; 2) proper feeding practices emphasizing the avoidance of saliva-sharing practices; 3) the timing of beginning oral hygiene and proper practices for this; and 4) the importance of the first dental visit by age 1 year.

3) Distributes an illustrated review of the important elements for good infant OH.

6.2 Administration of Intervention

The interventions will be delivered by the trained CP facilitators in the CP sessions. There are 2 intervention modules, a maternal module and an infant module. These will be delivered within CP groups in the intervention arm only. Each module lasts about 15 minutes. All women in the CP group in the intervention arm will be invited to receive the intervention regardless of their participation status (yes vs. no) in the study. CP group sessions are usually conducted with 2 clinicians, a facilitator and co-facilitator. CP group sessions take place in a closed room with the women and clinicians sitting on chairs in a circle.

6.3 Procedures for Training Interventionists and Monitoring Intervention Fidelity

Facilitators attend a 2-3- hour training session, typically conducted in a group setting. The training has 3 components:

1) A didactic session led by Dr. Berens (PI) that covers the rationale for the CPOP intervention and the evidence base for the components of the CPOP intervention modules including learning objectives and activities.

2) A step-by-step walk through of implementing the CPOP intervention (discussion and hands-on activities) by CP Consultant Laurie Jurkiewicz.

3) A role play session of the intervention modules using the intervention materials presented by Ms. Jurkiewicz.

4) Question and answer period to discuss integration of the modules into the routine CP sessions, issues that facilitators see arising in their groups, etc.

We had originally planned that facilitators would do an intervention practice session in a non-study CP group. However, we learned that the facilitators' group schedules are varied and not reliably scheduled closely enough together to be able to have a "practice" group and a study group in close proximity timewise. We therefore revised the plan in the following manner. The facilitators will conduct a practice session with study staff role playing as CP mom participants. Facilitators receive feedback and suggestions from research staff as needed.

Facilitator presentation of each CPOP intervention module is audio recorded and assessed by the study research staff for completeness of presentation of the intervention objectives. The research assessment of the audio recordings includes the following: Dr. Adams will train 1 CRA to complete the intervention fidelity scoring assessment; will establish inter-rater reliability; then do a final check by evaluating 4 audio recorded sessions and again comparing both sets of ratings for reliability. If the inter-rater reliability on the 4 evaluations is $\geq$85%, we will designate the CRA to score the subsequent audio recordings. Reliability refreshers will be conducted and re-assessed annually.

6.4 Assessment of Subject Compliance with Study Intervention

The skills-building activities for the women (tooth brushing and the Eastman toothpick test) will include practicing them during the intervention period. During the maternal module session, the facilitator will observe the women while they practice brushing their teeth and will assist any women who do not appear to be doing it properly. Subsequently, at each of the remaining CP sessions, the women will complete the toothpick test at their check-in time and will review the results with their facilitator. Also, following the module deliveries, the facilitator will complete a brief adherence checklist

to indicate whether each woman participated actively in the module activities. Women who do not attend an Intervention session or do not participate will be considered missing and will be retained in the ITT analysis. Missed attendance at OH module sessions will be considered a protocol deviation.

7. STUDY SCHEDULE

7.1 Screening and Recruitment

A study staff member will attend the second CP session to provide a brief overview of the study and invite women to seek further information by staying after the session or providing contact information for a follow up phone call. Eligibility will be described: women enrolled in CP care will be eligible to participate in CPOP if they are free of any condition that requires them to take antibiotic or antibacterial medicine prior to dental examinations or treatment. Women may enroll on that same day by staying after the CP session to have questions answered and to sign consents, or they could be enrolled at the time of follow-up phone contact. Women enrolled by phone can complete informed consent using the REDCap and DocuSign systems or can receive consent forms via email which they can review and bring with them to Visit 1 and sign prior to completing baseline data collection activities.

7.2 Baseline Data Collection (Visit 1, Day 0)

Women will be recruited between the 2nd CP session and the 3rd CP session (See Section 7.1). Visit 1 Data Collection procedures will be scheduled in that same time period to occur prior to the presentation of the CPOP maternal intervention module that will be conducted at Session 3. Consent will be verified and documented. Inclusion criteria will be confirmed. Both intervention and control groups will complete the following:

- Questionnaire assessments (demographics, oral health status, oral health knowledge, attitudes, behaviors
- Saliva specimen collection
- Dental examinations

7.3 Intermediate Visits

7.3.1 Visit 2 (Day 14 ± 14) Maternal Intervention Administration

The range of +/- days is broad because the baseline data could be collected in a range of approximately 28 days between CP sessions 2 and 3, but prior to the administration of the CPOP Maternal Module in CP Session 3.

- Takes place among participants in the Intervention arm only

- Administer the maternal OH module in Intervention Arm
- Record participation and attendance at the intervention

7.3.2 Visit 3 (Day 84+/- 15): Post-Maternal & Pre-Infant Intervention Data Collection

- Takes place prior to administration of the CPOP Infant Module occurring in Session 7 or 8
- Post-Maternal Intervention and Pre-infant Intervention questionnaire assessments
- Dental Examinations

7.3.3 Visit 4 (Day 90 +/- 21) Administer Infant Module in Intervention Arms

- Administer Infant Intervention
- Record attendance

7.3.4 Visit 5 (Day 109 +/- 21): Post-Infant Intervention Data Collection

- Collect post-infant intervention and participant acceptability assessment questionnaires

7.4 Final Visit 6 (Day 474 +/- 90)

Data collection at infant approximate 12 months of age

- Questionnaire assessments
- Maternal salivary bacterial assay specimen collection
- Infant salivary bacterial assay specimen collection

7.5 Withdrawal Visit

Women who withdraw from the study will be queried to determine their reasons for withdrawal.

7.6 Unscheduled Visit

N/A

8. STUDY PROCEDURES /EVALUATIONS

8.0 Procedures/Evaluations adaptations to comply with UCSF requirements and guidelines for conducting research with human subjects during the COVID-19 pandemic

As mentioned above in Section 6, we are not currently conducting any research activities with human subjects. Prior to resuming activities, we will work with the UCSF IRB, the UCSF School of Dentistry, and each clinical location's oversight leadership to determine and adhere to all safety guidelines and requirements associated with implementation and completion of our study activities. These include the collection of the following research data: in person on-line questionnaires, dental examinations including periodontal probing, saliva specimen collection from mothers and from their infants when they are approximately one-year of age at the 1-year follow up.

8.1 Study Procedures/Evaluations

Table 1: Assessment variables

Primary (1°) Outcome Variables	Measures	Base-line	Mid-Study1	Mid-Study2	Final 12 mo.
Maternal Oral Health • Gingival Status	• Periodontal pocket depth • Bleeding on probing	X X	X X		
Maternal Oral Hygiene • Oral Hygiene	• Plaque Index	X	X		
Infant Oral Health • Bacteria levels	• Salivary MS				X
Secondary (2°) Outcome Variables	**Measures**				
Maternal OH-related • Knowledge, Attitudes Behaviors	• Questionnaire	X	X		X
Infant OH-related • Knowledge, Attitudes, Behaviors of the mothers	• Questionnaire		X	X	X
Infant Oral Health • Bacteria levels	• Salivary LB, TVC				X
Descriptive (D) variables	**Measures**				
• Demographics	• Questionnaire	X			
• Maternal periodontal status	• Clinical attachment levels	X			
• Maternal caries	• ASTDD BSS untreated caries	X	X		
• Maternal bacteria levels	• Salivary MS, LB, TVC	X			X

Table 1 describes the components of the assessments, outcome variables, and measures. TVC= total viable count

QUESTIONNAIRE AND CLINICAL EVALUATIONS

- Questionnaire assessments:

We will collect questionnaire data via electronic survey completion at 4 time points in the study, using REDCap, a clinical trials management software program. For participants who request, the CRA will administer the questionnaires verbally.

1. Baseline: Demographic; Pre-Maternal questionnaire

   This includes basic demographic information, self-reported OH status, dental care utilization, OH knowledge, attitudes, and practices. It takes approximately 15 minutes to complete. Items on the questionnaire have been used in previous studies in similar populations[27], including the pilot study, and determined to be acceptable.

2. Mid-Study 1: Post-Maternal (1) and Pre-Infant questionnaire

   The first post-maternal assessment is a repeated measure of the baseline maternal assessment. The pre-infant assessment includes questions regarding knowledge about infant oral health, attitudes, proper infant oral hygiene and feeding practices, and self-efficacy items to prevent infant OH problems.

3. Mid-Study 2: Post-infant questionnaire (1); Participant Acceptability

4. Final 12-month post-partum: Post-Maternal (2) questionnaire; Post-Infant questionnaire (2); Participant Acceptability

   The second post-maternal and post-infant assessments are repeated measures.

- Dental examinations: Dental examinations will be conducted at baseline prior to the maternal module, and at Mid-Study 1 (following the maternal module and prior to the infant module). There are three components: 1) Plaque Index; 2) gingival assessment including bleeding on probing, pocket depths, and clinical attachment levels (attachment levels at baseline only); 3) need for treatment and referrals for dental care based on the ASTDD Basic Screening Survey.

  A portable dental unit will be utilized for the dental exams. It will be set up at the CP clinic in a space where the privacy of the procedure and confidentiality of any results will be maintained. The dental unit includes a patient chair, examiner chair, and assistant chair. No radiographs will be taken. The total examination will take approximately 15 minutes. A trained and calibrated dentist or dental hygienist will conduct all dental exams. The trained dental assistant/research assistant will be responsible for setting up supplies, entering data into the laptop computer, and providing proper storage and security of all data.

Prior to starting the exam, the examiner will screen the participant for the presence of any contraindications for receiving a periodontal exam. These include requiring antibiotic prophylaxis prior to a dental procedure due to the following heart conditions: 1) artificial heart valves; 2) a history of infective endocarditis; 3) a cardiac transplant with abnormal heart valve function; or 4) certain specific, serious congenital heart conditions (unrepaired or incompletely repaired cyanotic congenital heart disease including those with palliative shunts and conduits; a completely repaired congenital heart defect with prosthetic material or device for the first six months after the repair procedure; or any repaired congenital heart disease with residual defect such as persisting leaks or abnormal flow, at the site or adjacent to the site of a prosthetic patch or a prosthetic device). We are retaining the screening activity to assure that women have not acquired any contraindication subsequent to enrolling in the CPOP study. In the event that a woman has acquired a contraindication by the time of the second dental exam, she will remain a study participant and will receive only the plaque evaluation and Need for Treatment assessments.

A Microsoft Access electronic data entry program for dental exams (updated from the original CPOP pilot study) will be utilized for data capture. Other equipment and supplies will include mouth mirrors, periodontal probes, gauze, disposable gloves, eye protection, and other barrier protection for proper infection control. Reusable instruments will be sterilized at the UCSF School of Dentistry. Universal infection control guidelines and procedures will be followed.

The dental examination includes three procedures:

1. Oral Hygiene - Plaque Index (PI)

Plaque recording is important as a diagnostic, preventive, and treatment aid. For this study, we will use a modified plaque index (PI) developed by Silness and Löe, 1964[28].

Criteria for Plaque Index are the following:

0 No plaque
1 A film of plaque adhering to the free gingival margin and adjacent area of the tooth. Plaque may be seen in situ only with disclosing solution or probing. (Light plaque)
2 Moderate/heavy accumulation of soft deposits within the gingival pocket, or on the tooth and the gingival margin. Can be seen with the eye without using an instrument.

2. Gingival assessment: Gingival status will be assessed with full-mouth exams by measuring gingival recession and probing pocket depth to derive periodontal clinical attachment levels; and gingival bleeding on probing at baseline and post maternal module intervention. Changes in gingival status related to changes in oral hygiene (probing pocket depth and bleeding on probing) can be detected within the time frame we have designated for our pre-post dental examination. While attachment levels will be measured at baseline to characterize the sample, only probing pocket depth and bleeding on probing (not attachment levels) will be measured at mid-study post-maternal intervention.

3. Need for treatment and referrals for dental care: Though not a study outcome measure, as an obligation and service to the participants we will determine the need for treatment based on the protocol detailed in the Basic Screening Survey (BSS) developed by the Association of State and Territorial Dental Directors (ASTDD)[29]. For adults, the indicators include cavities, adults with one or more of their own teeth (as opposed to false teeth), and urgency of need for dental care.

   Criteria for determining dental treatment need are the following:

Category	Recommendation for next dental visit	Criteria
Code 2: Urgent or emergency need for dental care	As soon as possible	Signs or symptoms that include pain, infection, swelling, or soft tissue ulceration of more than two weeks duration (determined by questioning)
Code 1: Early dental care is needed	Within several weeks	Caries without accompanying signs or symptoms, individuals with spontaneous bleeding of the gums, suspicious white or red soft tissue areas, or an ill-fitting denture are coded “1”
Code 0: No obvious problems	Routine dental care (next regular checkup)	Any patient without above problems

   Oral health status information and recommendations for dental care will be provided to the participant along with a list of local dentists/dental clinics accepting Medicaid insurance and pregnant patients.

- Saliva collection: Saliva will be collected from the mother at baseline and both mother and baby at 12 months postpartum. It will be carried out by the CRA at a location and time convenient to the participant. The CRA will be trained in the following salivary collection techniques by Co-Investigator Dr. Ling Zhan.

Stimulated saliva collection from the mother: Two ml of stimulated saliva will be collected from mothers at least 2 hours after tooth-brushing or any food or beverage consumption. The mothers will be asked to chew on a wax tablet (Ivoclar Vivadent Inc., NY, USA) and expectorate into a test tube until 2 ml of stimulated saliva are collected.

Swab sample collection from the infant: An oral swab sample will be obtained from the child: 1) at least 1 hour after the last feeding and; 2) at least 2 hours after cleaning of the oral cavity. Sterile cotton-tipped applicators (CITMED Citronelle, AL) will be swabbed over the gingiva, tongue, oral mucosa, and tooth surfaces until the swab is saturated with saliva. The tip will be broken off and dropped into a pre-labeled 5 ml sample tube with 2 ml of reduced transport fluid (RTF)[30,31].

The test tubes containing saliva from the mother and child will be specially coded and no subject identification information will be used. The samples will be transported on ice by the RA to the microbiology laboratory at UCSF for total viable count (TVC), mutans streptococci (MS), and *lactobacillus* (LB) plating and culture within 24 hrs.

PROCESS EVALUATION OF IMPLEMENTATION

We will track participation and completion rates for purposes of evaluating implementation. These rates will be utilized to establish overall CPOP implementation fidelity and overall rate of assessment procedure completion. **(See Section 11 Statistical Considerations)**

Components of implementation	Definition of components[32] (Based on Linnan and Steckler, 2002)
Reach (Recruitment/Participation rate)	The proportion of women who are recruited, enrolled, and participate out of all invited women
Dose delivered (Delivery rate)	CPOP modules - proportion of planned sessions that were conducted
Dose received (Attendance rate)	Proportion of the CPOP modules that participants received
Fidelity (Estimated fidelity rate)	Proportion of the learning objectives addressed in the CPOP modules

8.2 Laboratory Procedures/Evaluations

8.2.1 Clinical Laboratory Evaluations

None

8.2.2 Special Assays or Procedures - Salivary bacterial analysis

Microbiological assays: Salivary assays will be performed under the guidance of Dr. Ling Zhan in her laboratory at UCSF. Maternal and infant saliva will be assayed for *Mutans Streptococci* (MS), Lactobacillus (LB), and Total Viable Count (TVC).

8.2.3 Specimen Preparation, Handling, and Storage

Saliva specimen storage, handling and banking for future studies: Each saliva sample will be labeled with study ID and collection date. Once transported to the microbiology lab, the samples will be plated immediately or stored in a 4º refrigerator for plating within 24 hours, all under the care and supervision of Dr. Zhan. The saliva samples will be destroyed according to biological hazardous waste guidelines immediately following the microbiological assays. The access to the samples will be logged in a laboratory log sheet. No saliva will be banked for future studies.

8.2.4 Specimen Shipment

Specimens will not be shipped

9. ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Because participants represent vulnerable populations, special attention will be given to any adverse events that occur during the study. The CPOP takes place in the health care setting in which participants receive their prenatal care. The CP facilitator who conducts the CPOP intervention in each CP group (participant's prenatal care provider) will be present and aware of each woman's physical condition during the CPOP study. Safety reporting for the study will focus on serious adverse events (SAEs) or unanticipated problems related to study interventions that occur during the course of the study.

9.1.1 Unanticipated Problems (UP)

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

AEs will be recorded and monitored to ascertain their frequency, severity, and nature, to determine whether they are related to study activities, and thus would reflect an Unanticipated Problem, which would be reported.

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 or dental 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

UPs will be recorded in the data collection system throughout the study.

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

9.3 Characteristics of an Adverse Event

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.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

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

Federal regulations and the UCSF IRB/HRPP require investigator reporting of any post-approval research-related event or information that may meet the HRPP's institutional definitions of "unanticipated problem involving risk to participants or others" or "serious or continuing noncompliance." The IRB/HRPP reviews the reports and determines whether they meet the institutional definition of a UP, among other things.

9.4.1 UP Reporting to IRB and NIDCR

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 AE, or any other incident, experience, or outcome as an UP 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, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to NIDCR within 5 working days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to NIDCR within 10 working days of the investigator becoming aware of the problem.
- All UPs 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 UPs will be reported to NIDCR's centralized reporting system via Rho Product Safety:

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

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

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

9.5 Halting Rules

If an UP develops that is a significant threat to the safety of participants, or if the number of SAEs overall or the number of occurrences of a particular type of SAE raises concerns, the NIDCR may temporarily suspend enrollment until a safety review is convened. The objective of such a review would be to decide whether the study should continue per protocol, proceed with caution, be further investigated, be modified and then continued, or be discontinued.

10. STUDY OVERSIGHT

In addition to the PIs' 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 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 NIDCR's Clinical Research Operations and Management Support (CROMS) contractor. The monitor will evaluate study processes and documentation based on NIDCR standards and the International Council for Harmonisation (ICH), E6: Good Clinical Practice (GCP) guidelines.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by the CROMS contractor, in collaboration with the NIDCR Office of Clinical Trials and Operations Management (OCTOM) and the NIDCR Program Official. The CMP will specify the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject 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 the CROMS contractor 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, OCTOM, and the NIDCR. The NIDCR reserves the right to conduct independent audits as necessary.

Monitoring visits will include, but are not limited to: review of site assessment and staff training; human subjects protection; protocol compliance; regulatory compliance; laboratory SOPs and compliance; laboratory sample disposition, storage, and handling; quality assurance; adverse event reporting; and integrity of research data and samples.

12. STATISTICAL CONSIDERATIONS

12.1 Study Hypotheses

Primary Hypothesis 1: Women in CP groups that include the CPOP intervention as part of their CP prenatal care will have significantly greater improvement in clinical OH and hygiene outcomes during pregnancy (reduced % sites bleeding on probing (BOP), reduced % sites with probing depths ≥4mm (PD4), reduced Plaque Index (PI) scores compared to women receiving CP usual care.

Primary Hypothesis 2: Infants of mothers in CP groups that include the CPOP intervention as part of their CP prenatal care will be significantly less likely to have the presence of salivary MS at age 12 months, compared to infants of mothers receiving CP usual care.

Secondary Hypothesis 1: Women in CP groups that include the CPOP intervention as part of their CP prenatal care, compared to women receiving CP usual care will have significantly greater increases in:

A. Maternal OH knowledge, attitudes, and hygiene behaviors during pregnancy;
B. Maternal infant-related OH knowledge and attitudes during pregnancy at 12 months postpartum; and
C. Maternal OH practices with their infant at 12 months postpartum.

Secondary Hypothesis 2: Infants of mothers in CP groups that include the CPOP intervention as part of their CP prenatal care will be significantly less likely to have the presence of salivary LB at age 12 months, compared to infants of mothers receiving CP usual care.

Secondary Hypothesis 3: Maternal OH knowledge, attitudes, and/or behaviors will result in significant mediation of the relationships between intervention arm and maternal OH (plaque levels, BOP and PD4) and infant OH risk (salivary bacteria incidence) outcomes.

12.2 Sample Size Considerations

Sample size estimate and power analyses. We assume 80% power; two-tailed α=0.05; 75% retention at 12 months; binary outcomes describing maternal gingival 1) pocket depth ≥4mm (PD4) and 2) bleeding on probing (BOP) at each probed site (max=168; in pilot data $\bar{x}$=159 sites per participant); 3) a continuously coded maternal plaque index score (PI: range 0-4); and 4) a child-level binary MS colonization indicator. The PD4 and BOP data for mothers will have a 5-level nested structure with a) 5 CP sites, b) 2-5 CP facilitators per CP site for a total of 14 CP facilitators participating in the study, c) 3-4 CP groups per facilitator for a total of 49 CP groups with participants enrolled in the study, and, on average, e) 8 study-enrolled mother-child dyads per CP group, and f) 159 gingival probe sites per mother; the maternal PI data and the child-level MS data will share the first four levels. The total sample size estimate is 392 mother-child dyads (49 CP groups $\times$ 8 mother-child dyads/CP group results in a total of 392 month-child dyads). Power analyses assumed two randomized groups including 8 and 6 CP facilitators, respectively. From our pilot data, we estimated intra-cluster correlations (ICC) for maternal PD4 equal to 0.001 for CP sites, facilitators, and groups, as well as 0.13 for CP women; ICCs for BOP equaled 0.04 for CP sites, facilitators, and groups, as well as 0.27 for CP women; ICCs for maternal PI equaled 0.13 for sites and 0.14 for facilitators and groups; ICCs for the child MS outcome equaled 0.01 for CP sites and CP facilitators as well as 0.04 for CP groups.

	observed effect in pilot	min. detectable effect
BOP: Ctrl v Intv (mothers)	16.7% v 10.7% OR=1.67, power>0.97	16.7% v 11.8% OR=1.50, power=0.80
PD≥4mm: Ctrl v Intv (mothers)	20.4% v 17.0%* OR=1.25, power=0.80	20.4% v 17.0%* OR=1.25, power=0.80
PI (means) Ctrl v Intv (mothers)	0.95 v 0.76 *d*=0.41, power=0.89	0.95 vs 0.78 *d*=0.37, power=0.80
MS: Ctrl v Intv (children)	24.9% v 6.5% OR=4.77, power=0.97	24.9% v 10.9% OR=2.71, power=0.80
* observed and minimum detectable effects equivalent w/in rounding; *d* represents a group difference of standardized means		

We present power to detect the effect sizes observed in our pilot study as well as the minimum detectable effects with 80% power. We note that although the observed effect on MS (OR=4.77) is considered 'large,' two reasons to choose the proposed design are that it, conservatively, is capable of detecting a 'medium' sized effect on MS (OR=2.71) and, more importantly, it is capable of detecting the smaller effect sizes anticipated on maternal outcomes. For the mediation test to help explicate mechanisms of action we further assumed a correlation of 0.30 between experimental groups and a unit-standardized continuous mediator describing maternal OH behavior: the minimum detectable indirect effect of experimental groups on the binary child MS indicator corresponded to an OR=1.30[33]. Power was calculated by simulation via multilevel logistic models with Laplace estimation; the simulations also suggested that for the proposed experimental design, the modeling framework produces unbiased parameter and standard error estimates.

12.3 Planned Interim Analyses (if applicable)

No planned interim analyses.

12.4 Final Analysis Plan

Proposed statistical analyses: Descriptive analyses will estimate means and proportions, measures of variability, and confidence intervals (CIs). We will determine whether participant baseline characteristics are independent of intervention group assignment (randomization check) and attrition (attrition analysis).

Missing data. Case-wise deletion of missing data will not be used for analysis because it relies on the relatively strong *missing completely at random* assumption and entails a loss of statistical power. Instead, multiple imputation will allow models to be fit to all available data and will invoke the relatively mild assumption that the data are *missing at random*, conditional on modeled variables[34-37].

Primary Analyses will include intention-to-treat comparisons**.** The multilevel data structure will be accommodated by generalized linear mixed models (GLMMs) with random intercepts for CP centers, facilitators, groups, mothers/children, and repeated assessments (for maternal outcomes; PROC GLIMMIX). Main outcomes include binomial indicators of mothers' BOP (# sites bled/# sites probed) and PD4 (# sites with ≥4mm pocket depth/# sites probed,) continuous indicator of maternal plaque levels, and a binary outcome of child oral MS colonization (multilevel logistic regression via Laplace estimation); and a count of child MS colonization (multilevel zero-inflated Poisson or a zero-inflated negative-binomial model, as appropriate, via Laplace). Each maternal outcome will be regressed onto indicators of experimental groups and assessment time, as well as the group-by-time interaction. Child MS outcomes at 12-months will be regressed onto the experimental group indicator. Significant intervention group main effects at follow-up and group-by-time interaction effects will be interpreted and described. If any key demographic or risk factors are imbalanced at baseline, we will include a quintile-stratified propensity adjustment, which can significantly reduce bias[38-40]. Propensity scores will be estimated by regressing the intervention group indicator onto baseline characteristics of participants (averaged up to the unit of randomization); covariate balance across groups will be assessed[41]. Next, propensity score quintiles will be formed. Regression models will initially include a quintile-by-groups-by-time interaction term to test whether the intervention effect is equivalent across quintiles. A significant interaction term would suggest quintile-specific treatment effects, which would then be estimated and reported. If the interaction term is non-significant, then it would be removed and the intervention effect estimated, conditional on the propensity-quintile main effect.

Secondary analyses will include multilevel linear models of secondary outcomes: OH knowledge, self-efficacy, importance, behavior scores; and multilevel binary and zero-inflated count outcome models of child LB and TVC levels. Additional multilevel models will explore whether any intervention effects are moderated by maternal race/ethnicity,

language, socioeconomic status, CP site, and baseline maternal OH knowledge and behaviors.

Mediation analyses to help assess mechanisms of action: We will test whether experimental group assignment impacts subsequent hypothesized maternal OH behavior mediators measured at the mid-study assessment period, as well as whether indirect effects of intervention groups on child MS outcomes via the candidate mediators are significant. Mediation will be tested with a series of linear, binary, and zero-inflated multilevel models, as appropriate, using methodological extensions to accommodate binary mediators and outcomes[42-44]. A draft interim analysis plan will be developed in case the U01's DSMB requires interim analyses; an alpha-spending function with O'Brien-Fleming rule will be proposed to control Type I error.

Descriptive analyses of facilitator perceived feasibility and acceptability of the CPOP intervention within CP clinics and group sessions: When study activities have been completed in the CP sites, Intervention facilitators will complete acceptability and feasibility assessments. The purpose of these is to provide evaluation of the perceived impact of the CPOP interventions integrated into CP sessions in terms of value to CP moms, value to the CP programs, and burdens/challenges (time constraints, adjusting topic schedules) versus benefits in CP groups.

13. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. No patient medical records will be accessed. 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 include informed consent forms. Informed consent will be obtained and maintained within the REDCap system which utilizes the IRB-approved DocuSign mechanism associated with REDCap for participant signature completion. Paper forms will be utilized when the REDCap system is not available and will be kept in locked file cabinets, separate from all other participant records. The web-based Clinical Trials Management Software (CTMS) system REDCap will be the original source for scheduled and actual study visits; dental examination data; questionnaire data; adverse event reports, and protocol deviations. Salivary assay data will be recorded in a lab notebook and entered electronically into REDCap.

Whenever possible, data will be entered directly into a computer. 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 Data Manager (DM) will serve as the Quality Management Coordinator, and in coordination with the Clinical Research Coordinator (CRC), will utilize clinical trials monitoring systems available through REDCap, NIDCR, and/or CROMS 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 CRC and CRA trainings, facilitator interventionist trainings, dental examiner trainings and calibration sessions and results, partner clinic preparations) and study activities (including participant recruitment, clinical partner site activities, activities completion including intervention deliveries by sites and by CPOP participant, CRF completion, 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. UCSF CRA staff 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 UCSF CRA staff. Participants will complete consents in REDCap and sign them using DocuSign. Documentation of informed consent will be maintained in REDCap.

C. Assessment completion. All CRC and CRA 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) CRAs will be trained to administer questionnaires and will enter the completion dates into the monitoring system, which will be verified by the REDCap data 2) The examiner will conduct the exam and the CRA will enter dental exam data into an Access database and document the completion of exams into REDCap. 3) CRAs will collect saliva specimens and will document in REDCap their completion and delivery to the clinical lab.

D. Intervention training, delivery, and fidelity monitoring. CPOP interventions will be delivered by CP facilitators who are trained by study investigators/personnel and evaluated for fidelity to the training plan. Training binders and toolboxes will be utilized to increase standardization and fidelity. Facilitators will conduct a practice session with study staff serving as intervention recipients, and receive feedback on the facilitator presentation of the intervention. All trainings will be documented and facilitators will receive refresher training annually. New facilitator CPOP interventionists will receive the same training. All actual intervention sessions will be documented and audiotaped for fidelity monitoring purposes. Facilitators will receive feedback to address any issues

identified in the fidelity evaluation. (More details can be found in the Intervention Training and Fidelity Manual).

E. Dental examiners training and calibration. Dental examiners will attend trainings and calibration sessions conducted by our Periodontal Co-Investigator team of Drs. Kapila and Lin. Trainings will be focused on conducting the Plaque Index, gingival measures of bleeding on probing, periodontal pocket depths, clinical attachment levels, and the ASTDD Basic Screening Survey protocol. Calibrations will be conducted for the Plaque Index and Periodontal pocket depth probing levels. Examiners will undergo initial training and calibration and recalibrated annually. Calibration participants will be recruited from the UCSF Campus Area and will include adults 18 years and older who are free of any condition that requires them to take antibiotic or antibacterial medication prior to dental procedures.

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 forms, recruitment materials, and all subject materials swill be submitted to the IRB at UCSF for review and approval. Approval of both the protocol and the consent forms must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the UCSF IRB 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 agreeing to participate in the study and continues throughout study participation. Consent forms will be required for the calibration participants, CP facilitator participants, and CP women participants, who also consent for their babies in their original baseline consent forms. Reconsent for the baby is necessary only in the event of a protocol change. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject via email or on paper. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. Study participants will include both English and Spanish speakers. Spanish language consent

forms will be provided and the CRAs recruiting in Spanish-language CP groups will be fluent Spanish-speakers. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates 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 subjects for their records. The rights and welfare of the subjects 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.

The consent process will be documented in REDCap.

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

The proposed CPOP clinical trial participants will include facilitators of the CP prenatal program, pregnant women, and eventually, their newborn infants. There are no exclusion criteria involving gender status. Males are not excluded, but it is unlikely that there will be male facilitators in the CP organization. However, if there are male facilitators, they will be eligible for participation in the study. All the CP women will be pregnant females. We will enroll all eligible infants of participating mothers, female and male.

15.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to subjects.

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

The study monitor or other authorized representatives of the 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 subjects. The clinical study site will permit access to such records.

A slight risk of disclosure of confidential information exists including dental exam results, salivary bacterial levels, and oral health behaviors. 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. They 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 CPOP trial. No identifying information will be transmitted from the clinical site or UCSF to NIDCR or the DSMB.

15.6 Future Use of Stored Specimens and Other Identifiable Data

N/A

16. DATA HANDLING AND RECORD KEEPING

The Principal 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 subjects, including accurate case report forms (CRFs), and source documentation.

16.1 Data Management Responsibilities

Staff will utilize a secure web-based data-entry and clinical trials management software (CTMS) 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. Multiple methods will be used to secure the electronically gathered data. 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. Operating system and software updates will be performed on a routine basis to ensure systems are hardened against hacking attempts.

Daily server backups will be performed. Data are stored using encryption. The servers are housed in the UCSF Medical Center data center (ECDC), providing state-of-the-art physical and electronic security. REDCap servers are guarded by multiple firewall and intrusion detection systems. Backup data files are kept in a secured environment and are available for recovery.

16.2 Data Capture Methods

Questionnaires will be self-administered in English or Spanish directly into REDCap with either the text presentation or upon request administered to them through an interview process. Dental exam results will be directly entered into an Access database that will be saved in Excel spreadsheets and then uploaded into the REDCap system. Any system modifications or refinements will be validated. Later, lab results of salivary assays,

including levels of MS, LB, and TVC, will be recorded in Excel spreadsheets as CFU/ml along with sampling date, processing date, counting date, and then uploaded into REDCap. 16.3 Types of Data

Informed consent will be collected electronically except in the cases of no internet access when paper consents will be used and stored as the source document. Electronic case report forms will include dental examination data (periodontal measurements, plaque levels, caries prevalence), questionnaire responses, and salivary assay data as well as completion of intervention and assessment activities.

16.4 Schedule and Content of Reports

Periodic reports documenting study progress will be generated by REDCap and reviewed by PIs 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 exam) that were missed; (iv) a report with graphical and tabular summaries of cumulative (versus planned) accrual and follow-up visit attendance; and (v) a report summarizing dental exam data collected.

Reports will be presented to the DSMB on a schedule that they determine.

16.5 Study Records Retention

The study will maintain participant records including data from dental exams and salivary assays from pregnant women and their babies. These records will be retained based on recommendations from the NIH, or if no guideline is established, based on the UC Vice Provost for Research guideline, which is that records be kept for 7 years after a child reaches the age of maturity (18 in California) for minors, and for 25 years for pregnant women.

16.6 Protocol Deviations

Protocol deviations and violations are unplanned deviations/violations from/of expected protocols. Protocol violations are serious unplanned occurrences that could reduce the quality of the data, for example a scheduled intervention module that did not take occur. Protocol deviations include study activities that occur outside of expected parameters that are not considered a threat to the quality of the data. For example, a scheduled intervention module that did not occur in the planned session but was delivered in a subsequent CP session would be identified as a protocol deviation. Other examples include assessment activities that a participant does not complete within the expected window or misses completely. Facilitator-level protocol violations and deviations will be recorded initially in Excel and monitored in REDCap. Participant-level deviations will be recorded directly in REDCap. All will be reported to the NIDCR, UCSF IRB, and the DSMB, according to their requirements.

17. PUBLICATION/DATA SHARING POLICY

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

If determined to be a condition for publication, the CPOP trial will be registered in a public trials registry such as *ClinicalTrials.gov*, per the International Committee of Medical Journal Editors (ICMJE) policy.

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 described was supported by Award Number 1U01DE027340-01from 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."

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

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. These standards can be reviewed online at *http://www.icmje.org/*.

SUPPLEMENTAL MATERIALS

With the exception of the Schedule of Events included in Appendix A, the listed documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately.

Appendix A: Schedule of Events (included)

Manual of Procedures

Data Management Plan

Quality Management Plan

Intervention Training and Fidelity Manual

Questionnaire assessments

Consent forms

Dental Examination Training and Calibration Manual

APPENDIX A: SCHEDULE OF EVENTS

Assessment variables, measures, and time points

Primary (1°) Outcome Variables	Measures	6 months												1 year
		CP sessions 2-10/Assessment time points												
		2	BL	3	4	5	6	MID 1	7	8*	MID 2	9	10	Post-partum 12 mo.
Maternal Oral Health • Gingival Status	• Periodontal pocket depth • Bleeding on probing		1° 1°	MM				1° 1°	IM					
Maternal Oral Hygiene • Oral Hygiene	• Plaque Index		1°	MM				1°	IM					
Infant Oral Health • Bacteria levels	• Salivary MS			MM					IM					1°
Secondary (2°) Outcome Variables	**Measures**													
Maternal OH-related • Knowledge, Attitudes Behaviors	• Questionnaire		2°	MM				2°	IM					2°
Infant OH-related • Knowledge, Attitudes, Behaviors of the mothers	• Questionnaire			MM				2°	IM		2°			2°
Infant Oral Health • Bacteria levels	• Salivary LB, TVC			MM					IM					2°
Descriptive (D) variables	**Measures**													
• Demographics	• Questionnaire		D	MM					IM					
• Maternal periodontal status	• Clinical attachment levels		D											
• Maternal caries	• ASTDD BSS untreated caries		D					D						
• Maternal bacteria levels	• Salivary MS, LB, TVC		D	MM					IM					D

MM Maternal Module IM Infant Module (may be delivered in Session 7 or 8*)

BL=baseline assessment; MID=mid-study assessments

Bibliography and References Cited

1. Laine MA. Effect of pregnancy on periodontal and dental health. *Acta odontologica Scandinavica.* Oct 2002;60(5):257-264.

2. American Dental Association Council on Access Prevention and Interprofessional Relations. Oral Health Care Series: Women's Oral Health Issues 2006; *http://www.ada.org/sections/professionalResources/pdfs/healthcare_womens.pdf* . Accessed September 19, 2012, 2012.

3. Armitage GC. Bi-directional relationship between pregnancy and periodontal disease. *Periodontology 2000.* Feb 2013;61(1):160-176.

4. Zeeman GG, Veth EO, Dennison DK. Focus on primary care: periodontal disease: implications for women's health. *Obstet Gynecol Surv.* Jan 2001;56(1):43-49.

5. Weintraub JA, Finlayson TL, Gansky SA, Santo W, Ramos-Gomez F. Clinically determined and self-reported dental status during and after pregnancy among low-income Hispanic women. *Journal of public health dentistry.* Jul 25 2013.

6. Chung LH, Gregorich SE, Armitage GC, Gonzalez-Vargas J, Adams SH. Sociodemographic disparities and behavioral factors in clinical oral health status during pregnancy. *Community dentistry and oral epidemiology.* Apr 2014;42(2):151-159.

7. Hwang SS, Smith VC, McCormick MC, Barfield WD. Racial/ethnic disparities in maternal oral health experiences in 10 states, pregnancy risk assessment monitoring system, 2004-2006. *Maternal and child health journal.* Aug 2011;15(6):722-729.

8. California HealthCare Foundation. Denti-Cal Facts and Figures. Oakland, CA: California HealthCare Foundation; 2010.

9. Dye BA, *Mitnik GL*, *Iafolla TJ*, *Vargas CM*. Trends in dental caries in children and adolescents according to poverty status in the United States from 1999 through 2004 and from 2011 through 2014. *J Am Dent Assoc.* 2017 Aug;148(8):550-565.e7.

10. Tanzer JM, Livingston J, Thompson AM. The microbiology of primary dental caries in humans. *J Dent Educ.* Oct 2001;65(10):1028-1037.

11. Tinanoff N, O'Sullivan DM. Early childhood caries: overview and recent findings. *Pediatr Dent.* Jan-Feb 1997;19(1):12-16.

12. Kohler B, Andreen I, Jonsson B. The effect of caries-preventive measures in mothers on dental caries and the oral presence of the bacteria Streptococcus mutans and lactobacilli in their children. *Arch Oral Biol.* 1984;29(11):879-883.

13. Li Y, Caufield PW. The fidelity of initial acquisition of mutans streptococci by infants from their mothers. *J Dent Res.* Feb 1995;74(2):681-685.

14. Berkowitz RJ. Mutans streptococci: acquisition and transmission. *Pediatr Dent.* Mar-Apr 2006;28(2):106-109; discussion 192-108.

15. Thorild I, Lindau-Jonson B, Twetman S. Prevalence of salivary Streptococcus mutans in mothers and in their preschool children. *Int J Paediatr Dent.* Jan 2002;12(1):2-7.

16. Berkowitz RJ. Causes, treatment and prevention of early childhood caries: a microbiologic perspective. *J Can Dent Assoc.* May 2003;69(5):304-307.

17. Kohler B, Andreen I. Influence of caries-preventive measures in mothers on cariogenic bacteria and caries experience in their children. *Arch Oral Biol.* Oct 1994;39(10):907-911.

18. da Silva Bastos Vde A, Freitas-Fernandes LB, Fidalgo TK, et al. Mother-to-child transmission of Streptococcus mutans: a systematic review and meta-analysis. *Journal of dentistry.* Feb 2015;43(2):181-191.

19. Binks C, Duane B. Mother-to-child transmission of Streptococcus mutans. *Evidence-based dentistry.* Jun 2015;16(2):39-40.

20. Oral Health Care During Pregnancy Expert Workgroup. Oral health care during pregnancy: a national consensus statement. Washington, DC: National Maternal and Child Oral Health Resource Center; 2012.

21. IOM (Institue of Medicine) and NRC (National Research Council). Improving access to oral health care for vulnerable and underserved populations. Washington, DC: The National Academies Press; 2011.

22. Ickovics JR, Kershaw TS, Westdahl C, et al. Group prenatal care and perinatal outcomes: a randomized controlled trial. *Obstetrics and gynecology.* Aug 2007;110(2 Pt 1):330-339.

23. Ickovics JR, Kershaw TS, Westdahl C, et al. Group prenatal care and preterm birth weight: results from a matched cohort study at public clinics. *Obstetrics and gynecology.* Nov 2003;102(5 Pt 1):1051-1057.

24. Adams, SH, Gregorich SE, Rising, SS, Hutchison, M, Chung LH. Integrating a nurse midwife-led oral health intervention into CenteringPregnancy® prenatal care: results of a pilot study. *J Midwifery Women's Health*. 2017; 62(4):463-469

25. Hayes RJ, Moulton LH. *Cluster randomised trials*. Boca Raton: CRC Press; 2009.

26. Caton JG, Polson AM. The interdental bleeding index: a simplified procedure for monitoring gingival health. *The Compendium of continuing education in dentistry.* Feb 1985;6(2):88, 90-82.

27. Adams SH, Hyde S, Gansky SA. Caregiver acceptability and preferences for early childhood caries preventive treatments for Hispanic children. *J Public Health Dent.* Fall 2009;69(4):217-224.

28. Silness J, Loe H. Periodontal Disease in Pregnancy. Ii. Correlation between Oral Hygiene and Periodontal Condtion. *Acta Odontol Scand.* Feb 1964;22:121-135.

29. Association of State and Territorial Dental Directors. Basic Screening Surveys: an approach to monitoring community oral health1999.

30. Hoover CI, Newbrun E. Survival of bacteria from human dental plaque under various transport conditions. *Journal of clinical microbiology.* Sep 1977;6(3):212-218.

31. Mundorff SA, Eisenberg AD, Leverett DH, Espeland MA, Proskin HM. Correlations between numbers of microflora in plaque and saliva. *Caries research.* 1990;24(5):312-317.

32. Steckler AB, Linnan L. *Process evaluation for public health interventions and research*. 1st ed. San Francisco, Calif.: Jossey-Bass; 2002.

33. Vittinghoff E, Sen S, McCulloch CE. Sample size calculations for evaluating mediation. *Stat Med.* Feb 15 2009;28(4):541-557.

34. Little RJA, Rubin DB. *Statistical analysis with missing data*. 2nd ed. Hoboken, N.J.: Wiley; 2002.

35. Rubin DB. *Multiple imputation for nonresponse in surveys*. New York ;: Wiley; 1987.

36. Schafer JL. Analysis of incomplete multivariate data. *Monographs on statistics and applied probability 72*. London ; New York: Chapman & Hall,; 1997: https://ucsf.idm.oclc.org/login?url=*http://uclibs.org/PID/31008*.

37. Rubin DB. Inference and missing data. *Biometrika.* 1976;63:581-592.

38. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med.* Oct 15 1998;17(19):2265-2281.

39. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983;60:41-55.

40. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *Journal of the American Statistical Association.* 1984;79:516-524.

41. Rubin DB. Using propensity scores to help design observational studies: application to the tobacco litigation. *Health Serv Outcomes Res Methodol.* 2001;2:169-188.

42. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol.* Dec 1986;51(6):1173-1182.

43. Li Y, Schneider JA, Bennett DA. Estimation of the mediation effect with a binary mediator. *Stat Med.* Aug 15 2007;26(18):3398-3414.

44. Albert JM. Distribution-free mediation analysis for nonlinear models with confounding. *Epidemiology.* Nov 2012;23(6):879-888.