Community Intervention to Reduce Tobacco Use Among Alaska Native Pregnant Women

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General Study Information

Principal Investigator: Christi A. Patten, Ph.D.

Study Title: Community Intervention to Reduce Tobacco Use Among Pregnant Alaska Native Women

Protocol version number and date: Version 9 – April 18, 2019

Purpose

Aims, purpose, or objectives:

Purpose:

Developing effective tobacco cessation interventions during pregnancy for American Indian and Alaska Native (AI/AN) people is a national priority and will contribute to the U.S. public health objective of reducing tobacco-related health disparities. Cancer is the leading cause of death among Alaska Natives and lung cancer is the leading cause of all cancer deaths for both men and women. In the U.S., the prevalence of cigarette smoking during pregnancy is 14% with the highest rates observed for Alaska Native (36%) and American Indian (21%) women. Prenatal use of smokeless tobacco (ST) is <0.05% among U.S. women. In the Yukon-Kuskokwim (Y-K) Delta region of southwest Alaska where the proposed project will take place, 79% of Alaska Native women smoke cigarettes or use ST during pregnancy. In addition, pregnancy appears to be a high-risk period for initiation of tobacco use, primarily ST, among women reporting no use of tobacco 3 months before

pregnancy. Both cigarette smoking and ST use during pregnancy pose substantial risks to maternal and fetal health. Moreover, about half of U.S. women who quit smoking due to pregnancy relapse by 6 months postpartum and up to 70% relapse within 12 months of childbirth. Except for our pilot study, interventions to reduce tobacco use during the prenatal or postpartum period have not been evaluated among AI/AN women.

This project builds on our successful 17-year partnership with the Alaska Native community focused on reducing tobacco use among pregnant women and youth. The team has conducted intervention research in Bethel and Anchorage, Alaska including our recently completed R01 grant with Alaska Native teens. In a previous pilot study, our results suggested that an individual-based intervention delivered at the first prenatal visit had low reach to pregnant women and poor tobacco abstinence rates. Intervention efforts targeting the entire community, not only pregnant women, to address social norms about tobacco use may be more effective. Thus, we propose to evaluate the efficacy of a novel, multi-component, theory-based intervention for reducing tobacco use during pregnancy, incorporating both individually targeted and community level components delivered by female Alaska Natives "Native Sisters." The intervention will build upon on effective community and individual-based approaches for tobacco cessation, efficacious lay health advisor approaches for cancer prevention among AI/AN women, and the strengths and values of the culture. The intervention also comprises a social marketing campaign including digital stories and other small media. This 6-year project "Healthy Pregnancies Study" has two phases, both approved by Mayo Clinic IRB and Alaska tribal reviews. Phase I is now completed including the analyses and development of a manuscript that was approved by the YKHC HSC. Phase II is ongoing

In Phase I, we developed and pre-tested the social marketing campaign messages and delivery channels through focus groups and individual interviews of pregnant women, family members, and Elders. The focus group work assessed reasons for initiating or continuing tobacco use during pregnancy and the potential role of other community members in addressing tobacco use in pregnancy. Findings were used to develop campaign messages and media that were pre-tested through individual interviews and refined. Session content for the individually targeted intervention components was also developed to align with the campaign messages. Finally, the "Native Sisters" were hired and trained to deliver the intervention. In Phase II, we will conduct a cluster randomized trial with village as the unit of assignment with a control comparison condition to test the efficacy of the intervention on tobacco use during pregnancy and postpartum. This protocol modification updates Phase I results and activities as well as procedures for Phase II.The Aims for Phase II of the project are:

Aim 1. To evaluate the efficacy of the intervention compared with the control condition on the biochemically confirmed 7-day point prevalence tobacco use rate at week 36 gestation and at 6 months postpartum.

Hypothesis: Compared with the control condition, the intervention will be associated with significantly lower rates of tobacco use in late pregnancy (80% vs. 65%) and at 6 months postpartum (70% vs. 55%).

Aim 2. To examine the effect of the intervention on proposed social cognitive-theory based mediators of change including perceived social norms about tobacco use and self-efficacy for non-tobacco use.

Hypothesis: Intervention effects on tobacco use at week 36 gestation and at 6 months postpartum will be mediated by perceived self-efficacy and anti-tobacco norms.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc.*):

Tobacco use during pregnancy and the postpartum period is a major public health problem in the U.S. The adverse effects of cigarette smoking during pregnancy and after delivery on maternal, fetal and infant health are well documented. A number of studies also report adverse health risks of prenatal smokeless tobacco (ST) use

including increased risk for preterm birth, stillbirth, and low-birth weight. These potential adverse health outcomes are especially relevant for populations with a high prevalence of tobacco use, including Alaska Native people. In Alaska, the prevalence of cigarette smoking (40% vs. 20%) and ST use (11% vs. 4%) is higher among Alaska Natives than White adults. The prevalence of cigarette smoking, ST, and any tobacco use during pregnancy is 26%, 17%, and 41% for Alaska Native women compared with 15%, 0.4%, and 16%, for White women respectively. The highest rates of prenatal ST use (56-60%) are observed for females residing in southwest Alaska including the Y-K Delta region. Among 832 Alaska Native women from this region, 48% used tobacco in the 3 months before pregnancy, 79% reported prenatal tobacco use and 70% used tobacco at 6 weeks postpartum. The increase in tobacco use in the prenatal period was largely accounted for by a significant ($p<0.001$) increase in ST use from before pregnancy (from 14% to 60%). Of the 432 women reporting no use of tobacco 3 months prior to pregnancy, 324 (75%) reported use during pregnancy, of which 78% used ST. Alaska Native women report lower spontaneous quit rates during pregnancy and higher relapse rates postpartum than White women. Thus, intervention efforts to reduce tobacco use during pregnancy and the postpartum period among Alaska Native women are significant.

Use of ST is an accepted cultural norm among women in many rural Alaska Native communities. A common form of ST used is Iqmik, a mixture of tobacco leaves and fungus ash. The addition of ash raises the pH of the tobacco increasing the amount of free (unionized) nicotine available for absorption and the available levels of carcinogens. Moreover, the maternal and neonatal serum cotinine concentrations were found to be significantly higher for mothers who used Iqmik compared to those using other forms of tobacco. Our qualitative work indicates that Iqmik is perceived as safer to use during pregnancy than cigarette smoking, and there is a low level of knowledge about adverse health effects of ST use. Studies conducted in the Y-K Delta region documented that Iqmik and other tobacco products are not used for ceremonial reasons.

The proposed research addresses a substantial gap in the field. Aside from our pilot study, tobacco use interventions have not been evaluated for AI/AN women during pregnancy or the postpartum period. Our pilot study suggested that an individual-based intervention delivered at the first prenatal visit had low reach to pregnant women and poor tobacco abstinence rates. These findings, along with our qualitative work, led us to consider an intervention incorporating both individually targeted and community level components focused on changing social norms about tobacco use in pregnancy through use of local female Elders "Native Sisters," an approach found to be effective for cancer prevention and control efforts among AI/AN women. In longitudinal studies, strong perceived anti-tobacco norms are predictive of smoking cessation at the population level and community-based interventions designed to influence social norms are effective for reducing smoking prevalence. Across a range of disease prevention behaviors, community interventions using social marketing to tailor messages to specific populations and incorporating outreach by influential community members, e.g., lay health advisors or popular opinion leaders, are particularly effective.

In Phase I, we developed and pre-tested the social marketing campaign messages and delivery channels using mixed (qualitative and quantitative) methods. Specifically, we completed the focus groups and individual interviews of pregnant women, family members, and Elders. We also developed the digital stories in collaboration with nDigiDreams, and finalized all other campaign materials in collaboration with Northwest Strategies, our marketing design company. In Phase I, focus groups and individual interviews were conducted in Bethel, Alaska with a targeted sample size of 60. Participants were recruited through press releases, radio advertisements, flyers and presentations. A total of 88 Alaska Native adults were screened, and 60 (68%) were eligible, consented to participate and showed for the focus group/individual interview. The sample comprised 23 pregnant women, 26 family members and friends (16 females, 11 males), and 11 Elders (6 females, 5 males).

A Yupik female from Northwest Strategies along with the study coordinator facilitated the focus groups. A translator was also present.

The qualitative analysis revealed that tobacco use during pregnancy is a top concern in the community. In addition, stress during pregnancy was a very common concern and thus providing advice to pregnant women on stress management may be helpful. Other health behaviors thought to be important to emphasize in any promotional campaign were eating healthy/nutrition and physical activity. The need for social support from the spouse or baby's father along with family members and friends is also important to help women stay tobacco free. Reasons for using Iqmik during pregnancy are women do not want to be judged and it's easier to hide than cigarettes, they do not have to go outside to use tobacco, and many believe it is safe to use. We also learned that Facebook was a way to obtain and give information to people, thus for the individual interviews we used Facebook as one avenue for recruitment. Finally, Elders were viewed as credible to advise pregnant women and to be advocates in the community at large.

Northwest Strategies designed 6 different posters to show participants in the focus groups. The posters represented emotional appeals and fact-based appeals to not use tobacco in pregnancy. The focus group participants preferred fact-based appeals to emotional appeals. They wanted to see graphic pictures on what happens to a baby when the mother uses tobacco, i.e., scare tactics. They wanted words and pictures that had "shock" value in contrast to what has been seen in the community before that reflected a "softer" approach.

Based on the focus group findings, Northwest Strategies designed three concepts (brochures) to test in the individual interviews. The three concepts represented fact-based, spiritual-based, and emotional-based appeals, respectively. The interviews used primarily close-ended questions to yield quantitative data. Participants were asked to rank the 3 concepts to rate each one on items assessing overall appeal and cultural relevance.

Study staff conducted individual interviews in-person, with a targeted sample size of 50. Participants were recruited through Facebook, press releases, flyers, presentations, and booths in hospital waiting areas. A total of 56 Alaska Native adults were screened, 55 (98%) were eligible, and of these 52 (95%) consented to participate. The sample comprised 20 pregnant women, 21 family members/friends (11 females, 10males), and 11 Elders (5 females, 6 males). The mean age was 39.6 (SD=17.3, range 19-78). Fifty six percent of participants currently used tobacco. With respect to extent to which participants follow the traditional Yupik way of life, 54% indicated "a lot," 44% reported "some" and 2% "not at all".

The fact-based concept was preferred by half (50%) of the sample, whereas 25% liked the emotion-based and 25% liked the spiritual-based concept best ($p=0.039$). The fact-based brochure illustrated the impact of maternal tobacco use along the progression from the fetus to adulthood. From this fact-based brochure, 64% reported that it was attention grabbing, and 69% indicated it was appropriate for Alaska Native people. If the brochure was displayed in the community, participants were very likely (39%) or somewhat likely (43%) to quit tobacco or encourage someone to quit. There were no significant differences in concept preference by study group (pregnant women, Elder, family member/friends), extent to which participants followed a Yupik lifestyle, or current tobacco use. For example, 52% of tobacco users and 48% of nonusers preferred the fact-based brochure. There were significant gender differences detected with most of the males preferring the fact-based brochure (81%) compared to 36% of females, $p=0.010$. Among females, however, preferences were distributed proportionately across the three concepts with a slight preference for the fact-based brochure (fact-based 36%, emotional brochure 33%, spiritual brochure 31%). Overall, findings from the quantitative interviews were highly concordant with our focus group results wherein participants preferred fact-based appeals to emotional appeals and wanted visual aids to understand the impact on children of using tobacco in pregnancy.

With respect to campaign promotional items, participants preferred baby items, e.g., bibs, blankets (38%) or hoodies (33%). The least preferred item was a pen (62% did not like this item).

To create the digital storytelling DVD, two workshops were held in Bethel, Alaska in January and February of 2015 and conducted by nDigidreams, Inc. The target sample was 10 participants (5 each workshop). A total of 12 people participated (3 males, 9 females). Of these, 9 were community members and 3 were health care professionals. Six of the stories were translated into Yupik. In addition, Northwest Strategies finalized and mass produced all other campaign material including posters, brochures, and promotional items.

Community and Study Setting

The community, Alaska Native people of Yupik or Cupik ethnicity residing in the Y-K Delta region (population 25,000), is fairly homogeneous with respect to culture and language with most residents fluent in both English and Yupik. The population is of low SES and most maintain a subsistence lifestyle. Bethel (population 6,000) is the hub for the 56 villages of this region (population 28-1,133). No road connects the villages and residents travel by small plane, boat or snow machine. A typical village has a combined elementary and secondary school, a local village council, health clinic, store, post office, church and community center. The Y-K Delta Regional Hospital (YKDRH), owned and operated by the Yukon-Kuskokwim Health Corporation (YKHC), is located in Bethel and provides health care for residents. The YKDRH employs 170 Alaska Native health aides who work in their home villages, with 1-8 per village based on its size. Prenatal care visits are scheduled at the YKDRH (96% of women receive prenatal care) including a visit at week 36 gestation. At this time, high-risk pregnancies are triaged for delivery at the Alaska Native Medical Center in Anchorage and women from the villages reside at the Bethel pre-maternal home until delivery. There is an average of over 600 births each year. A scheduled visit at 8 weeks postpartum is attended by 70% of women. As part of normal care, prenatal, obstetrical, and WIC providers routinely ask about tobacco use and provide brief advice to quit but more substantive cessation interventions are not provided. Less than 2% of pregnant women enroll each year in the YKDRH clinical cessation program.

CBPR Approach

This project involves Community Based Participatory Research (CBPR) methods from design through implementation and dissemination. The need for interventions focused on tobacco use during pregnancy came from the YKHC Board of Directors - Alaska Native leaders representing villages of this region, and YKDRH providers. In addition, community needs assessments were conducted through focus groups, individual interviews, and discussions with Elders and other key informants. This work involved building research capacity of our community partner staff through training in focus groups, analysis and dissemination of results. Recognizing other health issues facing residents of this region, the YKHC Board of Directors has made reducing tobacco use among pregnant women and children a top behavioral health priority. This research priority is consistent with the cultural value emphasizing the health and welfare of the children as paramount and guided the subsequent direction of our work. The design and focus of this project came from discussions and interactions over the past three years with leadership, providers, and community members. The YKHC Board of Directors will review, provide input, and approve the study materials and all dissemination activities at multiple stages of development.

All aspects of the project will be guided by a project-specific Community Advisory Committee (CAC) that was formed specifically for this project. While the number has varied over the course of the project, the CAC is comprised of about 10 professional and community members. We have communicated with CAC members through email as needed and during in-person meetings held on-site in Bethel, Alaska. The CAC reviewed, edited and approved all focus group and individual interview questions along with recruitment flyers as part of the Phase I activities, and approved the campaign material including the digital stories to be used in Phase II. We will continue to meet with the CAC as we prepare for and implement the randomized trial in Phase II. The CAC will continue to have an essential role in planning and guiding all project activities. They have met about once per year with the study team in Bethel. The meetings have been held over the noon hour where lunch is served. In addition, CAC members receive an honorarium for meeting participation.

Alaska Native females "Native Sisters" were hired to implement the intervention and may have a role in dissemination efforts.

Community members were recruited during Phase I for focus groups and interviews to assist in developing the campaign messages and intervention materials. Community members participated in creating the digital stories component of the intervention. We chose intervention components that build on the current system of care and materials that are readily transportable such as a digital stories DVD, posters, and brochures. Participatory methods will be used to disseminate the study findings.

Subject Information – charts, records, images, or specimens are considered 'subjects'

Target accrual: *Proposed number of subjects to be included in your study at your site. "Subjects" may include Mayo Clinic charts, records, or specimens,* ***and/or*** *charts, records, or specimens received at Mayo Clinic from external sources for collaborating analysis by the investigator under this IRB application*:

Subject population:

Phase I:

Phase I was completed, in which we developed the intervention, including a social marketing campaign and individually targeted intervention sessions. Focus group feedback was obtained from 23 pregnant women, 26 family members, and 11 Elders. This information was used to develop intervention concepts. Message concepts were then pre-tested using individual interviews with a different sample of 20 pregnant women, 21 family members and 11 Elders. Campaign materials and an outline for the individual sessions were also developed as part of Phase I. Sample sizes were based on recommendations for qualitative interviews with divisions based on the subsets (strata) in Table 1 below. However, for pregnant women we were not successful in recruiting subset B (current tobacco user but did not use before pregnancy, i.e., initiators).

Table 1: Phase I Focus Group and Individual Interviews Composition

Pregnant Women	**Family Members**	**Elders**
A. Tobacco user, used before pregnancy B. Tobacco user, non-user before pregnancy C. Non-tobacco user, used before	A. Female tobacco user B. Female non-tobacco user C. Male tobacco user D. Male non-tobacco user	A. Female tobacco user B. Female non-tobacco user C. Male tobacco user D. Male non-tobacco user

pregnancy D. Non-tobacco user both time periods		

Inclusion Criteria for the Focus Groups and Individual Interviews:

Participants consisted of 43 Alaska Native pregnant adults age 18 and older. To be eligible for Phase I of the study, Alaska Native pregnant women participants had to:

- Be 18 years of age or older
- Provide written informed consent
- Be willing to take part in a focus group or qualitative interview

A total of 47 family members/friends were recruited for both assessment portions of the study. The Alaska Native family members/friend participants had to:

- Live with or have at least weekly contact of any form (e.g., telephone, in-person) with a pregnant Alaska Native woman (did not need to be linked to a pregnant woman who participated in the focus groups/interviews)
- Be 18 years of age or older
- Provide written informed consent
- Be willing to take part in a focus group or qualitative interview

An Elder is defined as someone who is age 55 or older or a younger person in good standing with the community who was identified by local village councils or YKHC staff and Alaska Native. A total of 22 Elders were recruited for both assessment portions of the study. The Alaska Native Elder participants had to:

- Provide written informed consent
- Be willing to take part in a focus group or qualitative interview

Exclusion Criteria:

Individuals (i.e., pregnant women, family members/friends of pregnant AK Native, and community Elders) were considered ineligible to participate in either of the assessments if they are:

- Not Alaska Native
- Under the age of 18
- Unwilling to participate in the focus group or individual interview
- Refused to provide written informed consent
- A family member/friend who did not live with or have weekly contact with a pregnant Alaska Native woman

Inclusion Criteria for Native Sisters (hired as Interventionists for Phase II):

Over the course of the project, five Alaska Native women were hired to conduct the intervention. The Native Sisters are female, over the age of 55 or a younger woman who is in good standing in the community, no tobacco use in the previous six months, and have bilingual (English/Yupik) communication skills. It was not be feasible to select Native Sisters who have never used tobacco during pregnancy. To enhance their credibility, however, potential individuals were hired only if their beliefs about tobacco use during pregnancy were

consistent with the project goals as assessed by YKHC staff. We have experienced staff turnover over the course of the project. Currently, there are two Alaska Native women who serve as Native Sisters.

Phase II:

Target accrual:

In Phase II, we will conduct an evaluation of the intervention applying a group-randomized design with village as the unit of assignment. Sixteen villages were selected and randomly assigned to receive the intervention (8 villages) or control condition (8 villages) with ≥ 22 pregnant women recruited per village.

Subject population:

Sample size calculation. We estimate recruiting ≥ 22 pregnant women per village (N=352). Accounting for an estimated attrition rate of 10% due to miscarriage, abortion or fetal demise, we plan to achieve a final sample of at least 320 women eligible for follow-up. All pregnant women (tobacco users and non-users) will be eligible for enrollment.

Actual accrual. We met our targeted sample size of 352 women enrolled. Encouragingly, overall participation from control villages (n=164) was similar to overall participation from intervention villages (n=188). Although we estimated 22 or more women enrolled in each village, this was not feasible. Study villages were more or less interested in participating, with a range of 2 to 42 women enrolled in the 16 study villages.

Inclusion Criteria:

Participants consist of 352 Alaska Native pregnant adults age 18 and older. To be eligible for the study, Alaska Native pregnant women participants must:

- Be 18 years of age or older
- Provide written informed consent
- Currently 36 weeks or less gestation
- Access to a working telephone

Exclusion Criteria:

Individuals will be considered ineligible to participate in the study if they are:

- Not Alaska Native
- Under the age of 18
- Currently not pregnant or ≥ 37 weeks gestation

- No access to a working telephone
- Refuse to provide written informed consent

Will a Certificate of Confidentiality be obtained? *If yes, provide an explanation*.
No, a Certificate of Confidentiality will not be obtained.

Study Design

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:

Phase IA. Social Marketing Campaign Development

We used a social marketing planning framework consistent with the NCI guidelines for developing health communication programs addressing key components of message construction. We conducted two rounds of assessments to obtain feedback from community members to develop and pre-test the campaign messages and media. The first round utilized focus groups to understand perceptions and preferences of community members that will be used to develop concepts. For the second round, we pre-tested concepts of the campaign messages and materials. A different sample of participants was interviewed individually using primarily close-ended questions to generate quantitative summaries of preferences for campaign messages and materials. In addition to pregnant women, it was important to learn from others (family members, Elders) who may influence the decisions of and support women to use or not use tobacco.

Health Communication Framework

We used two frameworks to address the influence of culture in designing health messages, the cultural variance framework and the surface/deep structure framework. The cultural variance framework takes into account cultural influences on health behavior including identity affiliations (e.g., Yupik lifestyle) and cultural attributes such as specific beliefs, norms (i.e., communication styles), and values (i.e., family, relationships, collectivism). Surface and deep structure informs both the content and format of messages. Surface structure involves matching materials and messages to observable social and behavioral characteristics of a target population such as using music, clothing, and people familiar to and preferred by the target audience. It also involves identifying the channels (media) and settings (churches, school) that are most appropriate for the delivery of messages and programs. The second dimension is deep structure which is the level at which program and messages reflect the ways cultural, social, environmental, and historical factors influence health behaviors, e.g., cultural beliefs and values. An appropriate surface structure generally increases receptivity, comprehension and acceptance of messages whereas appropriate deep structure conveys salience. The cultural variance framework largely addresses the deeper level of components of tailoring messages.

Potential Media and Collaborators

We partnered with Northwest Strategies based in Anchorage, a respected Alaska Native-owned graphics design company with a connection to the Y-K Delta community and with expertise in designing effective social marketing campaigns using focus groups. We developed a campaign that includes small media (e.g., digital stories DVD, brochures) that will be distributed by the Native Sisters along with interpersonal communications (e.g., community presentations). Larger media, e.g., radio, television and newspapers, serve all villages in this region therefore it is not possible to manipulate mass media channels for the campaign in the randomized trial. Due to lack of home Internet/wireless access in the villages, it is not feasible to use iPods, computers, Smart Phones or other related technologies to deliver the campaign.

The digital stories DVD was produced by Brenda K. Manuelito, Director of nDigiDreams and well known for her work in AI/AN communities. We successfully partnered with nDigiDreams to develop a cancer prevention digital stories DVD for the Navajo Nation (CA152433). Digital storytelling is a participatory approach whereby community members provide 2-5 minute personal narratives along with digital images (i.e., pictures) and music to enhance their stories. Digital storytelling and other narrative forms of communication (e.g., photonovela, photovoice) have emerged as important tools for cancer prevention and control and are especially effective among AI/AN people with a strong oral tradition. Unlike videos, digital stories can be

easily edited and updated over time thereby enhancing cost-effectiveness. A DVD format is feasible for intervention delivery in this region; ≥90% of residents have access to a DVD player in their home.

Participants and Eligibility Criteria for Focus Groups and Individual Interviews

To enhance feasibility, all participants were recruited from the Bethel area. Although recruitment activities took place in Bethel, participants did not need to reside there to be eligible. Flyers were posted at Bethel grocery stores, restaurants, the YKDRH, Bethel pre-maternal home and other locations and included a toll-free study number. The study was also advertised in the "Tundra Drums," a region-specific newspaper; local radio stations; on the YKHC employee website and using social media (e.g. Facebook). The project was described as involving a discussion about healthy pregnancies and gathering ideas how communities can best support Alaska Native women to have healthy pregnancies. The research coordinator conducted a brief screening in-person or by phone to assess the eligibility criteria which was: (1) Alaska Native, (2) ≥18 years of age, and (3) able to provide written informed consent. Both tobacco users (defined as use of any form of tobacco at least once in the past 7 days) and non-users were eligible. Potential family members had to live with or have at least weekly contact of any form (e.g., telephone, in-person) with an Alaska Native pregnant woman, but did not need to be linked to a pregnant woman who participated in the focus groups/interviews. The term "family member" is broadly defined for this study because extended families are inclusive such that a close friend or cousin may be referred to as an auntie or grandma. The Elder participants had to be at least 55 years of age, and were recruited as described above or were selected by YKHC staff or CAC members.

Consent Process:

All participants provided written informed consent. The potential research participant was informed of the details of the study and the fact that participation was entirely voluntary and would not affect their current or future medical care at the Y-K Delta Regional Hospital or at any Alaska or Mayo Clinic facility. Each research participant was informed of the study and signed the written informed consent form before being enrolled in the study. This ensured that all participants met the inclusion/exclusion criteria as stated above and had provided written informed consent. The participants were given a copy of the informed consent form, which included written information on the nature of the study and alternatives to taking part. After the informed consent form was reviewed with the study participant, the participant was given time to ask questions and decide whether or not s/he wished to participate. After ensuring the participant clearly understood the study procedures and agreed to follow them, the participant was asked to sign two original copies of the informed consent form; one was for the participant and one is kept on site at YKHC with the study book. The informed consent form listed the telephone numbers (including 1-800 numbers) of the principal investigator for the study in which they enrolled and study staff to contact on-site in Bethel. Participants were encouraged to call anytime with concerns or problems that might occur during the study.

Focus groups

For the first round, we chose to use focus groups to allow for discussion of community norms, i.e., shared cultural meanings to inform the deeper structure. Focus groups are an acceptable and feasible means of gathering information from people in this region and are similar to the talking circle or sharing of personal stories. However, we provided the option of conducting an individual interview if scheduling or other barriers limited participation.

Development of the Moderator Guide and Training. A semi-structured focus group moderator guide was developed with our CAC based on our health communications framework, relevant literature and expert

recommendations. The topics are outlined in Table 2. The moderator guide was pre-tested with 3-6 individuals who met the eligibility criteria described above, and revised, prior to use.

Table 2. Focus Group Domains

1. Healthy pregnancy
- Personal views of what constitutes a healthy pregnancy
- Most important health concerns when pregnant, e.g., healthy baby, gaining weight, diabetes, high blood pressure
- General concerns during pregnancy, e.g., proper nutrition, getting to prenatal exams, handling stress
- Who supports woman during pregnancy

2. Knowledge of perceived health risks of Iqmik and other tobacco use
- Perceived risks of SHS exposure for families.
- Perceived risks of maternal Iqmik and other tobacco use for mother, fetus, and infant
- How pregnant women and others experience and perceive risk information
- Generational influences and social roles, e.g., grandmother and mother used Iqmik during pregnancy, perceptions of the history of use and when/why women began to use ST during pregnancy
- Processes involved for continuing to use tobacco in pregnancy vs. starting to use in pregnancy

3. Role of Family Members, Female Elders "Native Sisters" and other Community Members
- How best to utilize Native Sisters in delivering intervention.
- Role of spouse/partners/others influencing pregnant women's tobacco use
- Willingness of others to avoid tobacco use around pregnant woman, create tobacco free homes
- Readiness of community to address tobacco use, along with benefits and barriers

4. Culturally Relevant Campaign Messages and Media/Delivery Channels (using visual aids developed by Northwest Strategies)
- Preferences with respect to language, tone, cultural appeals (e.g., healthy pregnancies, well babies, future generations)
- Types of messages, e.g., best mechanisms to raise awareness of harms of tobacco use for prevention and cessation respectively
- Integrating other targets such as prenatal care utilization, wellness, stress, depression, alcohol use, physical activity
- Credible message sources, e.g., Elders/grandmothers/mothers/others
- Delivery channels–(a) interpersonal venues: optimal times, places, activities and venues for Native Sister outreach for presentations, discussions, and distribution of campaign media, e.g., bingo, schools, dances, church; (b) small media: e.g., preferred promotional items

To enhance translation of the qualitative findings to campaign development, the focus groups were co-facilitated by the YKHC research coordinator and a trained Yupik representative from Northwest Strategies. A Yupik translator (YKHC Nicotine Control staff member) was available during the focus groups and individual interviews.

The Mayo Clinic study assistant trained the YKHC research coordinator in focus group facilitation on-site in Bethel. Training was done using didactics, role-plays and mock sessions. A focus group manual covering basic interviewing style, how to respond to various questions or concerns that may arise during the focus group

process, as well as guidelines and expectations about interviewer behavior, was developed for this project. The research coordinator read the focus group manual and spent at least 6 hours practicing the skills described in the manual, and completed a certification interview.

Procedures.

Focus groups and individual interviews took place in Bethel in a YKDRH conference room and were audio taped. Prior to commencement of the focus group, the research coordinator obtained written informed consent and conducted an assessment individually and privately using an interview format to assess socio-demographics, tobacco use status, spouse/partner tobacco use status, and among tobacco users readiness to quit using the validated Contemplation Ladder. For pregnant women we also assessed length of gestation and parity. Each focus group lasted about 90 minutes and individual interviews about 40 minutes, and snacks and beverages were provided. We estimated 8 per focus group with pregnant women (N=32) and family members/friends (N=32), and 4 per group with Elders (N=16); for a total of 80 participants. Based on our experience, focus groups of this size are ideal for information sharing and individual participation in this region. However, it was not feasible to recruit large numbers of Elders for focus groups and we experienced scheduling difficulties. Thus, we offered the option of conducting an individual interview instead. Focus group/individual interviews were conducted with 23pregnant women, 26 family members and 11 Elders. Each participant received a $75 gift card.

Data from the focus groups was transcribed and analyzed by YKHC and Mayo research staff. The audiotapes were destroyed immediately after a written transcript was produced. Results and recommendations were reviewed and finalized with the CAC. The results were used by Northwest Strategies to develop three draft message concepts and promotional items that will be utilized in the social marketing campaign. The message concepts used different colors and illustrations along with text. Using readability analysis software, message concepts (text) were constructed at a 6^{th} grade reading level.

Individual Interviews

Next, individual interviews were used to pre-test the message concepts and promotional items.

Procedures.

Interviews were conducted by the research coordinator in-person and lasted about 30 minutes. Prior to the interview, the research coordinator obtained written informed consent. This was completed in person. All participants were shown draft message concepts and illustrations of promotional items for review in advance.

The interviews lasted an average of 21 minutes (range 10-60). As part of the interview, basic demographics and tobacco use were assessed. Multiple-choice response formats were used to assess each message concept and media's ability to attract attention (recall), convey its main point (comprehension) and create a positive response (reaction), in addition to salience and cultural acceptability. Participants were asked to rank order their preferences. Preferences for types of promotional items were also assessed. We conducted a total of 52 individual interviews (20 pregnant women, 21 family members and 11 Elders), with divisions based on the subsets in Table 1. Each participant received a $25 gift card.

Production of Campaign Media

Data from the individual interviews was analyzed by Paul Decker, biostatistician at Mayo Clinic. Results and recommendations were reviewed and finalized with the CAC. Results and recommendations were used by Northwest Strategies to finalize and produce all campaign media except for the digital stories DVD.

Promotional items (hoodie sweatshirts, post-it notes and baby bibs), posters, brochures, flyers, newsletters, and event displays have been created.

Digital stories DVD were developed by nDigiDreams and link to the key messages/themes identified in the formative work (focus groups and individual interviews). Ms. Manuelito and a co-trainer held two workshops in Bethel with a total of twelve participants. YKHC staff assisted in selecting potential "storytellers" with consultation from our CAC. Workshops were held over 3 days lasting about 4-8 hours each day. Participants signed a press release and received a $250 honorarium. Meals and beverages were also provided. Instructions were mailed to each participant prior to the workshop to bring a draft of their story of 1.5 pages or 250 words in length and photos/music they wish to incorporate. Participants shared their story in a story circle to help facilitate dialogue and obtain feedback to further develop their stories. After making revisions, participants individually recorded their story in a private room. nDigiDreams edited stories with each participant to create an integrated theme consistent with the campaign, with the final product about 20 minutes in length. Six of the stories were also translated into Yup'ik.

Phase IB. Native Sister Selection Criteria, Training, and Peer-Counseling Components

"Native Sisters" (defined above) were hired by YKHC to serve as the ambassadors of the social marketing campaign and other intervention components in their respective village for the randomized trial. Potential Native Sisters were identified by local village councils and YKHC staff with assistance from our CAC. Native Sisters were hired to implement the intervention in their home village but this was not always feasible. We were only able to find five Native Sisters who were tobacco-free and met our eligibility requirements. Thus, a Native Sister from one Intervention village may have been asked to conduct the intervention calls for other villages. In addition, one Native Sister from Bethel was hiredwho conducted the intervention for other villages. In addition, the YKHC research coordinator was trained as a back-up interventionist. During a period where there was no YKHC research coordinator hired, Mayo Clinic staff were assigned to deliver the intervention calls (20 women total). Currently, however, there are two Native Sisters delivering the intervention for all intervention villages. All intervention sessions with pregnant women are conducted via phone or in-person at the village Health Clinic.

The Native Sisters will be responsible for distributing all media to community members, e.g., handing out the digital stories DVDs and promotional items, and displaying posters. From our qualitative work we determined preferred interpersonal channels of communication/outreach by the Native Sister including community-wide presentations and hosting events (e.g., basketball tournament). We anticipate that the Native Sister will integrate her outreach with ongoing community events such as church activities, bingo and dances. Power point presentations and talking points/scripts have been developed for the Native Sisters and each will be provided with a laptop and portable LCD equipment. The Native Sister will seek advice from their village council on implementing the campaign and develop community contacts and volunteers who could assist. However, it has not always been feasible for the Native Sisters to conduct presentations or outreach activities, which reflects the current practice.

A manual was developed with a script/talking points for the Native Sisters to use during the six individual-based peer counseling sessions with enrolled pregnant women. The Study Coordinator will provide the woman with the campaign media including the digital stories DVD and brochures prior to the first session with the Native Sister. The content of the six sessions closely aligns with the campaign messages and address social norms about tobacco use. The sessions include evidence based techniques such as providing support, problem-solving, and reinforcement to pregnant women; emphasize use of positive cultural activities (e.g., berry picking) for coping with withdrawal/stress or preventing tobacco initiation; and emphasize other health topics in

pregnancy and postpartum such as reducing stress. Additional messages/strategies (i.e., manuals) were developed from our qualitative work geared toward cessation and toward preventing initiation, respectively. The manual was developed, refined and then streamlined using an iterative process with feedback from the Native Sisters during the course of the project.

A process evaluation checklist titled "Native Sister Event Totals" was developed for the Native Sisters to document delivery of specific community and individual level intervention components based on existing measures. Using a checklist, each Native Sister is asked to record distribution of media such as number of DVDs and brochures provided; and presentations/outreach activities and number of people in attendance. Individual-level components recorded will include number of sessions completed (6 total), format (telephone/in-person at the village clinic) and duration documented in the intervention manual.

Extensive training (2 days) was provided in Bethel to the Native Sisters as a group from Drs. Burhansstipanov (Consultant), Lando (Co-Investigator), Resnicow (Consultant), and Patten (PI). It will include an overview of the conceptual framework, roles and responsibilities, specific strategies for implementing and promoting the campaign, reviewing and personalizing scripts and power points to guide community presentations, and overview and practice with the process evaluation tool. Simulations and role-plays and a discussion of commonly asked questions were provided. A basic overview of tobacco use, maternal/infant health risks of tobacco use, and treatment referral options will also be covered. Using a peer protocol developed for several prior NIH studies, the Native Sisters were trained on basic communication skills such as open questions and reflective listening, and will be certified based on successful completion of mock test sessions. Refresher trainings were provided by the research team in Bethel (held by Drs. Patten, Lando and Resnicow) and more recently in Portland, Oregon (held by Dr. Linda Burhanstippanov).

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:

Community Partnership and Team

Collectively, the study team is uniquely suited to conduct the proposed project. Mayo Clinic investigators and YKHC staff have established and maintained a successful 17 year partnership. YKHC partners include Dr. Joseph Klejka (Alaska site PI) with expertise in public health approaches in the local community, Ms. Desnoyers (Project Manager) with expertise in the local community, Ms. Alexie (Research Coordinator) and Ms. Boyer (Collaborator) Vice-President Village Health.

The Mayo Clinic team includes Dr. Patten (PI) with experience in behavioral tobacco cessation intervention development and qualitative design and analysis, Ms. Hughes and Ms. Bock (Study Assistants) with experience clinical trials, and Mr. Decker, M.S. (Biostatistician). New collaborations were formed through developing this proposal. Dr. Lando (Co-I) has expertise in community-based interventions and interventions to reduce tobacco use during pregnancy and the post-partum period. Dr. Resnicow (Consultant) is an expert in designing health communications and cultural messaging, along with social marketing approaches to health promotion. Dr. Burhanstippanov (Consultant) has expertise in lay health advisor approaches to cancer prevention in AI/AN communities.

Media and Collaborators.

Northwest Strategies, based in Anchorage, is a respected Alaska Native-owned graphics design company with a connection to the Y-K Delta community and with expertise in designing effective social marketing campaigns using focus groups. Northwest Strategies developed all media for Phase I except for the digital stories. The digital stories DVD have been produced by Brenda K. Manuelito, Director of nDigiDreams and

well known for her work in AI/AN communities. The YKHC PR department will partner and contract with businesses of their choosing to develop any dissemination media, which will be reviewed and approved by the YKHC HSC and IRBs prior to its use.

Phase II. Randomized Controlled Trial

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:

We will conduct an evaluation of the intervention applying a group-randomized design with village as the unit of assessment. Sixteen villages were selected and randomly assigned to receive the intervention (8 villages) or control condition (8 villages) with an estimated ≥ 22 pregnant women recruited per village. Recruitment is completed. An average of 22 women were recruited per village, with a range of 2 to 42, due to varying levels of interest in participation across the 16 study villages. All pregnant women (tobacco users and non-users) were eligible for enrollment. Assessments will be completed by participants through 6 months postpartum. Figure 1 contrasts the study village conditions.

Figure 1. Design Elements	Control	Intervention
Usual Care: at time of positive pregnancy test done in the woman's village the Health Aide provides brief advice to quit (< 3 minutes) to women who use tobacco. Health aide gives all women (tobacco users and non-users) written materials on risks of tobacco use.	X	X
Health Aide or village clinic staff will provide the woman with a study flyer and asks her if she would like to learn more about the study. If yes, the health aide or clinic staff will provide contact information to the research coordinator.	X	X
Research coordinator screens the woman for eligibility.	X	X
Research coordinator consents and enrolls eligible/interested pregnant women and conducts a baseline assessment.		
Follow-up assessments conducted with enrolled women by the research coordinator at 12 weeks post-enrollment, at week 36 gestation, and weeks 8 and 26 postpartum.	X	X
Intervention Villages Only: Native Sister delivers a community-wide social marketing campaign in her home village over a 2-year period. Native Sister delivers 6 telephone based peer counseling sessions to enrolled women during pregnancy (weeks 1, 2, 4 post-enrollment) and postpartum (weeks 2, 4, 6)		X

Rationale for a Group Randomized Design:

We chose to use an experimental design to maximize internal validity. Our decision to utilize a group-randomized design is consistent with the format of intervention delivery at the community level and how the program would be broadly disseminated if effective. In addition, with individual randomization there is the potential for cross-contamination due to small village sizes and social mixing of intervention and control participants within villages. Intervention materials will be disseminated to the control villages after the final assessment. The homogeneity across villages with respect to cultural and social traditions as well as language enhances the external validity of the findings to this region and other rural areas of Alaska. Although the villages are relatively small in population size, this will allow for greater exposure of the community to the campaign messages and outreach by Native Sisters. Because villages differ on population size, we randomized villages within this stratum. We targeted villages other than Bethel for this trial. While Bethel is the largest village with respect to overall population size and number of pregnant women each year, it is not possible to randomize Bethel to study conditions due to the high likelihood of cross-contamination (i.e., with small media). Bethel serves as the hub for healthcare and other resources for village residents, as well as transportation to Anchorage. There is a small risk of contamination when enrolled women interact in Bethel for prenatal care visits or at the pre-maternal home.

Rationale for a 2-Arm Design:

It is well documented that tobacco abstinence is correlated with intervention dose. Thus, we considered a third study condition consisting of the social marketing campaign alone without individually targeted support.

However, there are not sufficient numbers of villages with enough pregnant women to make this approach feasible. A strength of our approach is that the intervention combines the most effective approach for community level and individual-based interventions, maximizing potential impact on tobacco use outcomes. Also, the program announcement required a multi-level intervention. Although the intervention is complex, the Mayo Clinic biostatistician will conduct a process evaluation to assess the woman's intervention exposure.

Rationale for Usual Care as the Control Condition:

The intervention provided by a health aide is the usual care provided to pregnant women in this region and will therefore serve as an appropriate comparison condition. From a scientific perspective, our control condition reflects the minimal counseling methods (Ask, Advise) recommended for pregnant smokers. Also, as a part of usual care, all pregnant women (tobacco users and non-users) will receive written materials on the risks of tobacco use during pregnancy. There is little evidence that providing written materials alone enhances cessation rates. The state of Alaska advertises the state quitline and other cessation resources on an ongoing basis throughout the Y-K Delta region. We considered providing a health promotion campaign in the control villages to equate the study conditions on extraneous factors such as contact time and attention, but decided against it based on feasibility and practice considerations associated with delivering a campaign in all 16 villages.

Intervention Reach, Delivery and Duration:

The earliest point of care is at the time of a positive pregnancy test. Even if the woman conducts a home pregnancy test, results are confirmed at the village clinic, and the health aide is responsible for scheduling prenatal care appointments. Another opportunity for recruitment will be at a prenatal visit in Bethel. Thus, our recruitment methods should reach most, if not all-pregnant women.

Our prior work indicated that female Elders (as defined above) would be most credible to deliver the intervention. Although it would be practical to have village-based health aides deliver the intervention, credibility is an issue because most health aides use tobacco. Research highlights respect for and credibility of Elders in the transmission of cultural knowledge and health information in AI/AN communities. Elders also encourage and reinforce community ownership of problems and problem solving, i.e., the cultural value of collective responsibility. Recruiting Elders from their home village will enhance the dissemination and sustainability of the intervention. Further, a local Elder is likely to be more credible and effective at changing social norms around tobacco use than one from another village. When we experienced difficulties finding a sufficient number of Native Sisters or during staff turnover we hired an individual residing in Bethel who delivered the intervention to other villages. In addition, someone hired in one Intervention village may have served as the "Native Sister" for another Intervention village. The study team has experience with hiring and working with village-based Elders/community members. Moreover, the YKHC study coordinator was trained as a back-up interventionist. During times of Native Sister staff turnover, and staff turnover with respect to the YKHC study coordinator, Mayo research staff was asked by prior YKHC managers overseeing the project to fill in (calls for 20 participants total were assigned to Mayo staff). Currently, however, there are two Native Sisters hired and assigned to make the intervention calls for all intervention villages.

Consistent with prior community-based studies, the social marketing campaign will last about two years (27 months). Native Sisters will attempt to contact all enrolled women for six telephone-based peer counseling sessions (3 during pregnancy, 3 postpartum). A face-to-face peer counseling session will be offered if it is

feasible at the village health clinic. We chose 6 sessions total based on evidence of a dose response relationship between number of sessions and successful tobacco use outcomes. While there is no evidence that pharmacotherapy is effective during pregnancy, use of NRT and other medications will be encouraged by the Native Sister during the postpartum period by referral to the YKDRH clinical cessation program.

Randomization:

We selected villages for participation in this study based on our prior work and established relationships, and villages that had sufficient numbers of pregnant women each year. In 2011, over a 9 month period there were 16 villages with at least 15 women seen for a 1st prenatal visit (Table 1). This estimate was conservative because it does not reflect all women with a positive pregnancy test. Sixteen villages were stratified based on village size (<600 and >600) and randomly assigned to receive the intervention (8 villages) or control condition (8 villages).

Table 1. Village count of pregnant women seen for a 1st visit Jan-Sept 2011 (excludes Bethel)

# pregnant women	# villages
1-9	20
10-14	9
15-19	7
20-25	8
26-30	1
31-35	0
36-44	3

The research coordinator and study staff met with the respective village tribal councils and village health aide staff of all 16 villages to enlist their participation. We have successfully used this approach in our previous group-randomized trial in this region.

Recruitment of pregnant women within each village will occur over an 25-month period. We attempted to enroll at least 22 pregnant women from each of the 16 villages, accounting for an estimated rate of attrition of 10% based on prior studies due to miscarriage, abortion or fetal demise, to achieve a final sample of at least 320 women eligible for follow-up. Recruitment delays were encountered and thus NIH funding was extended from 5 to 6 years (see Table 4). We will request a no cost extension from NIH for a 7th project year which will enable us to complete analyses and dissemination as remaining funds permit.

Recruitment:

A study logo that consists of a baby in womb and the text "*Healthy Pregnancies*" was created by Northwest Strategies. The logo was placed on all recruitment materials, and will be used on any communications from the research coordinator or study team members.

Recruitment procedures were developed through several face-to-face and videoconference meetings with YK leadership and village health aide staff. At the time of a positive pregnancy test or at any visit encounter with a pregnant woman, the village-based health aide or a YKHC staff member will briefly state that there is a healthy pregnancy study being done in the village and provide the woman with a 1-page flyer with study information and a toll-free number. The flyer will describe the study as a "Healthy Pregnancies Study" promoting proper nutrition and exercise, ways to reduce stress, social support, taking part in cultural activities, and education on tobacco use. Next the health aide or YKHC staff member will ask the woman if she would be interested in learning more about the study. If the woman indicates "yes", the staff will take the woman's name and contact information and inform the woman that the research coordinator will contact her to provide more details about the project. Each clinic will designate a staff member who will send the names and contact information of only the women who indicated they want to receive more information about the study to the research coordinator by electronic mail or phone on a weekly basis.

To implement these procedures, prior to commencing the trial, the YKHC program manager and YKHC study coordinator, along with the Mayo Clinic study staff, traveled to all 16 villages to meet with village health aides and other clinic staff. This was followed up by regular phone calls to the clinic, resulting in recruitment of

some participants through these methods. Village health aides sometimes assisted with recruitment by helping the participant mail or fax her consent form to the YKHC study coordinator. In the later stages of recruitment, however, it was not feasible for village based health aides to assist with recruitment.

Another point of recruitment was at a prenatal care visit in Bethel which was highly successful. During the study start-up period, providers from the Women's Health Department were informed about the study and asked to hand out a study flyer to any pregnant women. Posters with study information were also displayed at the Women's Health Department and at the Centering Pregnancy Offices along with the Pre-Maternal home. Per our discussions with Dr. Klejka, YKHC HSC Chair, flyers for the Bethel-based providers and posters displayed in Bethel had the names of all 16 participating villages so that only women from these villages would be encouraged to call for information. Another YKHC HSC approved method utilized information found within the YKHC electronic heath record (EMR) system medical records. An electronic report exists within the YKHC EMR that collates the future appointment dates of pregnant women who have been seen at least once already for a current pregnancy. This report included the pregnant patients: name, address, phone number, date of birth, current weeks gestation (at the report date) as well as the location and date of the last pregnancy-related medical appointment and the location and date of the next scheduled pregnancy-based appointment. Only YKHC employees had access to access, run, utilize, and subsequently discard the report. Mayo Clinic and other research staff that are not YKHC full-time regular employees did not view or access the report, nor any protected Health Information (PHI) associated with the report. YKHC study staff ran the report about once per week. Once the report was generated, it was filtered to show only Healthy Pregnancy Study-related village-based patients. These women were contacted via phone call to inform her of the study and/or mail her the general study postcard (Control postcard) directly to her address. This postcard was previously approved by the Alaska Area IRB and the YKHC HSC. YKHC study personnel were the only persons making this initial contact. If the patient stated that they would like additional information regarding the study after initial contact, this was documented on a tracking log and the follow-up contact may be made by either Mayo Clinic or YKHC study staff. The list was secured by the YKHC research staff (as with all study information) in a locked file cabinet at YKHC. To ensure that the handling of protected health information (PHI) remains a top priority, the YKHC Compliance Officer was consulted to ensure that this method met the standards for handling PHI.

Additionally, some women contacted the Native Sister to learn more about the study. The Native Sister shared the woman's name and phone number with the research coordinator who then contacted the woman to describe the study and enroll her if she is interested.

Other methods of recruitment included posting flyers throughout Bethel. These posters were the same design as the approved posters already being displayed at YKHC listing the 16 villages in the study. Facebook was found to be an effective method of recruitment for Phase I. In fact, we chose to implement Facebook recruitment for the Phase I individual interviews after initial advice from community members who participated in our Phase I focus groups. Therefore, during Phase II we posted study information on Facebook pages for the study villages. Each village has its own Facebook page and thus the risk of control participants learning about intervention aspects such as Native Sisters would be minimal. To enhance recruitment, generic study postcards were mailed to all households in the 8 control villages to ensure community members learn about the study. The postcards were mailed in a box from Mayo Clinic to YKHC Bethel to be postmarked then sent to each village post office for distribution.

We chose to limit enrollment to females aged 18 years and older as different individual-based interventions and age-appropriate assessments may be needed for adolescent tobacco users given their differing development and cognitive abilities. Only about 7% of pregnancies in the region are among girls <17 years of age. About 95% of Y-K Delta residents have access to a telephone in their home. Baseline tobacco users as

well as non-users were eligible to focus on prevention and cessation of tobacco during pregnancy and the postpartum period. Tobacco use status will be biochemically confirmed at baseline using saliva cotinine.

Consent process:

All participants will provide written informed consent. Participants completed the consent form in-person in Bethel or the consent form was mailed to the potential participant with a postage paid return envelope or faxed to the village health clinic. For those completing consent via mail, the study coordinator will review the consent form with the potential participant by phone. Each potential research participant will be informed of the details of the study and the fact that participation is entirely voluntary and will not affect their current or future medical care at the Y-K Delta Regional Hospital or at any Alaska or Mayo Clinic facility. Each research participant must be informed of the study and sign the written informed consent form before being enrolled in the study. This will ensure that all participants meet the inclusion/exclusion criteria as stated above and have provided written informed consent form before being enrolled in the study. The participant will be given a copy of the informed consent form, which includes written information on the nature of the study and alternatives to taking part.

After the informed consent form is reviewed with the study participant, the participant will be given time to ask questions and decide whether or not she wishes to participate. After ensuring the participant clearly understands the study procedures and agrees to follow them, the participant will be asked to sign two original copies of the informed consent form; one is for the participant and one is kept on site at YKHC with the study book. The informed consent form lists the telephone numbers (including 1-800 numbers) of the principal investigator for the study in which they are enrolled and study staff to contact on-site in Bethel. Participants will be encouraged to call anytime with concerns or problems that might occur during the study.

For those being consented via mail, they will sign two copies of the consent form, mail them to the coordinator in the postage paid return envelope they are provided. Upon receipt of the consent forms, the coordinator will then sign both copies of the consent, keep one for the study folder and send one copy to the participant.

Procedures:

After providing written informed consent, the woman was enrolled. Next, the research staffadministered a baseline interview by phone or in-person to assess socio-demographic information; nicotine dependence and readiness to quit (for tobacco users); theory-based measures (mediators), e.g., self-efficacy, social norms and cultural beliefs about tobacco use; and other variables targeted by the intervention such as second hand smoke exposure (See Table 2 below). These measures have established psychometric properties. Efforts will be made to obtain follow-up assessments from all participants by the research staff who does not provide the intervention. In-person assessments will occur when the woman is scheduled for an appointment in Bethel (at week 36 gestation (if enrolled before this time point) and at 8 weeks postpartum). The week 36 assessment will be attempted in-person at the Bethel pre-maternal home or by phone before or after delivery. All other follow-up assessments and for women whose in-person assessment is missed (e.g., due to pregnancy complications, triage to Anchorage for delivery, or lack of time at the visit), will be conducted by phone. The assessments are similar to those completed at baseline. Participants will receive a $25 gift card for completing each assessment at baseline and follow-up for up to a total of $125. Each assessment is estimated to last about 60 minutes.

Self-reported tobacco use will be assessed using a multiple choice response format recommended for pregnant smokers. A saliva specimen will be collected for analysis of cotinine from all participants and

analyzed using either a NicAlert test strip at point of contact or by mailing the saliva sample to Mayo Clinic, Rochester, MN, laboratories for analysis. The biospecimens will be labeled using only the assigned study ID number with no other identifiers. Biochemical confirmation of self-reported tobacco abstinence during pregnancy is recommended due to high rates of nondisclosure, and cotinine is the recommended biomarker. As in other Alaska-based studies, the research staff will mail the woman a packet with detailed instructions for collecting and returning the sample by mail, a process shown to yield specimens consistent with in-person collection methods. There is precedence for obtaining saliva samples by mail to confirm tobacco abstinence in previous trials. Specimen samples will be shipped to Mayo Clinic for analysis. The lab results will be sent to the research assistant Ms. Hughes at Mayo Clinic, Rochester for data entry. Once the specimen sample is processed and results posted, the sample will be destroyed immediately. We will assess NRT use at follow-up since use would elevate cotinine levels. Point-prevalence tobacco use will be defined as reported use of tobacco during the previous 7 days. For women who report no tobacco use, this will be confirmed with a salivary cotinine concentration of $\leq$ 20 ng/ml. Baseline tobacco users will be asked to report the number of quit attempts made and date of last attempt since enrollment. Also, baseline non-tobacco users will be asked to report any use and date of first use of tobacco since enrollment.

Table 2. Measures and Schedule of Assessments		**Pregnancy**			**Postpartum**	
DATA COLLECTED (Reference #)	# items	**Baseline**	**12 weeks** →	**Week 36 Gestation**	**Week 8**	**Week 26**
Socio-demographics (45)	10	X				
Self-reported tobacco use (3,149)	1	X	~~X~~	X	X	X
Saliva specimen for analysis of cotinine	--	X		X		X
Tobacco users only: FTND/FTQ-ST (nicotine dependence) (147,148)	6	X				
Tobacco users only: Contemplation Ladder (readiness to quit) (121)	1	X	~~X~~	X	X	X
Program evaluation	--		X →	← ~~X~~	X	X
Theory-Based Variables (Mediators) Self-efficacy to quit or not use tobacco (150)	14	X	~~X~~	X	X	X
Social norms about tobacco use (52)	6	X	~~X~~	X	X	X
Social support for non-tobacco use (151)	1	X	~~X~~	X	X	X
Other variables targeted Attitudes/perceived risks of Iqmik/tobacco use in pregnancy (66,152)	4	X	~~X~~	X	X	X
SHS exposure: tobacco use of spouse/partner and household members, home restrictions on tobacco use (153-155)	4	X	~~X~~	X	X	X
Treatment Self-regulation Questionnaire (TSRQ) (intrinsic vs. extrinsic motivation for change) (156,157)	15	X	~~X~~	X	X	X
Yupik Wellness Questionnaire (i.e., positive cultural activities) (101)	24	X	~~X~~	X	X	X
Perceived Stress Scale (158) and CES-D Depression Scale (159)	4/20	X	~~X~~	X	X	X
Prenatal care utilization (161)	2	X	~~X~~	X		

To reduce participant burden, the week 12 pregnancy assessment was reduced to only one form (program evaluation). No questions were added. We noted early in the follow-up phase that the week 12 assessment was not feasible to complete at the intended time frame. This is because most women enrolled at $\geq$ 24 weeks gestation, in which case the week 36 assessment coincides with the 12 week post-enrollment assessment. Of 352 participants enrolled, 222 (63%) were $\geq$24 weeks gestation at enrollment. Moreover, only 9% of women (33/352) enrolled before 12 weeks gestation. The consent form acknowledges that the week 12 assessment would be conducted depending on when they enroll in the study. To accommodate varying enrollment/ assessment schedules and to standardize the assessment process for research staff and participants, we will ask the week 12 program evaluation questions at the week 36 assessment, and participants will receive a gift card for completing each of these assessments. Thus, the potential number of gift cards provided and assessments conducted with participants will remain the same.

Intervention (Intervention Villages only):

Native Sister Intervention Components

Native Sister hiring and training:

Native Sisters were hired by YKHC as a sub-contracted employee. The Native Sister's role is one of a study ambassador for the Healthy Pregnancies Study in their village. Native Sisters must meet the following qualifications:

- Be considered an Elder: 55 years and older or someone who is younger but who is seen as credible in the community/or as a leader
- Speak both English and Yup'ik
- Tobacco-free (no tobacco use in the last 6 months)
- Believe that no tobacco use is safe when a woman is pregnant

The Native Sisters will report to the YKHC program manager or YKHC research coordinator (current practice) and will work in tandem with the YKHC research coordinator. In addition to the initial training, two refresher trainings were held (one in Bethel and one in Portland, Oregon) with the Native Sisters as a group to enhance support and facilitate sharing of "lessons learned". The Native Sisters will also meet with the YKHC research coordinator every week by telephone. Native Sisters will complete checklists of intervention components delivered on the Native Sisters Events Total form and turn these checklists into the YKHC research coordinator.

Individual components:

After enrollment and completion of baseline questionnaires, study staff provided the woman with the campaign material including the digital stories DVD and brochures in person or by mail. The YKHC research coordinator also shared the study participant's contact information with the Native Sister in the respective village. The Native Sister will contact the participant via phone to schedule their six telephone-based peer counseling sessions. The manual has been developed along with a script/talking points for the Native Sisters to use during the six individual-based peer counseling sessions with the study participants. The content of the six sessions closely aligns with the campaign messages and addresses social norms about tobacco use. The sessions include evidence based techniques including providing support, problem-solving, and reinforcement to pregnant women, emphasizing the use of positive cultural activities (e.g., berry picking) for coping with withdrawal/stress or preventing tobacco initiation; and emphasize other health topics in pregnancy and postpartum such as reducing stress. Any materials/resources (e.g., breastfeeding, nutrition, exercise, reducing stress) the pregnant woman is interested in receiving will be mailed to her by the research coordinator. The Native Sister will email or call the research coordinator informing her of the materials that need to be mailed to the participant. The manual was developed from our qualitative work geared toward cessation and preventing initiation.

Community components:

Additionally, the Native Sister will distribute all campaign media to community members (e.g., handing out the digital story DVDs and promotional items, and displaying posters). A power point presentation was developed for the Native Sisters. During the training the Native Sisters will individualize their presentation. The Native Sister will seek advice from the village councils on implementing the campaign and develop community contacts and volunteers who can assist. However, it has not been feasible for the Native Sisters to conduct presentations or outreach activities on a consistent basis, which reflects the current practice. YKHC

staff plans to conduct village travel whereby promotional and other campaign material will be distributed in the intervention villages.

A process evaluation checklist titled "Native Sisters Events Total" was created for the Native Sisters to document delivery of specific community and individual level intervention components based on existing measures. Using this checklist, each Native Sister will record distribution of media such as number of DVDs and brochures provided; and presentations/outreach activities and number of people in attendance. Individual-level components recorded will include number of sessions completed (of 6 total), format (telephone/in-person) and duration. These checklists will be provided to the YKHC research coordinator.

Campaign Materials:

All campaign materials and promotional items were created by Northwest Strategies, Inc., except for the digital stories DVD which was created by nDigiDreams, Inc. Both design companies are Native owned. A study logo "*Healthy Pregnancies*" was created by Northwest Strategies and was placed on all campaign materials. The materials to be distributed in the intervention villages are:

1) Posters
2) Flyers
3) Digital stories DVD
4) Promotional items: baby bibs, hoodies, and note pads
5) Brochure targeted to pregnant women

In addition, all village members in each of the 8 intervention villages were mailed an oversized postcard to ensure that all community members are exposed to the campaign. The postcards were mailed in a box from Mayo Clinic to each village post office for distribution. The postcards therefore did not have any names or identifying information.

Please note that the materials above were informed by the focus groups and individual interviews conducted among community members in the completed Phase I work. Specifically, participants preferred a fact-based approach that grabbed the attention from community members.

Data Management and Quality Assurance:

We will use the same coordination and communication procedures successfully utilized in our previous work including a weekly study team meeting held via teleconference. Dr. Patten and Mayo Clinic study staff provided training to the research coordinator on the study protocol on-site in Bethel.

All original participant forms are maintained in a locked file at the Healthy Pregnancies YKHC office. These forms with the exception of enrollment forms contain a study ID number only (e.g., no names or other identifying information). YKHC and Mayo Clinic study staff share the workload for assessments. For some period of time, a YKHC research coordinator was not hired and thus the program managers overseeing the project requested Mayo research staff to assist. The study staff from Mayo Clinic were added to the consent form as personnel modifications approved by the YKHC HSC as well as Mayo Clinic and Alaska Area IRB. The consent form allows for data sharing between Mayo Clinic and YKHC. An electronic data-tracking sheet with names and contact information is shared between Mayo and YKHC using a secure, encrypted email transfer.

When assessments are completed by YKHC, electronic (scanned) copies are transferred to Mayo Clinic Division of Biostatistics via secure encrypted email and stored on a secure server. Mayo Clinic staff enters data

into a secure REDCap (Research Electronic Data Capture) database that contains only the Study ID. Access to the information is restricted to the study statistician, Mr. Paul Decker, and study staff only. We will monitor quality control of the data through review of participant forms and procedures on-site in Bethel. Moreover, the biostatistician, Mr. Paul Decker, will perform monthly data checks and will also analyze the data. At both YKHC and Mayo Clinic, standard data security and monitoring procedures are in place. From the daily Native Sisters checklist, an implementation index has been created to permit exploration of dose response effects.

Program Evaluation:

For intervention villages, we will assess the pregnant woman's reported exposure to the social marketing campaign using continuous scales adapted from prior research. For example, her awareness/recall of the campaign messages and media (e.g., point of purchase displays), if she used/read various campaign media such as brochures and viewed the digital stories DVD, and if she shared these materials and/or the information with others in her village. An intervention exposure index will be created based on item responses to permit exploration of dose response effects.

De-identified data will be obtained from the YKDRH on the total number of positive pregnancy tests in each randomized village during the recruitment period. The study staff will track recruitment data, completion of each follow-up assessment among enrolled participants and use of NRT/other treatments.

To inform dissemination efforts, we will track and summarize the cost of intervention components including time spent by the Native Sisters and program materials displayed/distributed in each village. We will exclude development costs, as these would not be considered in disseminating the intervention.

Dissemination Plan To communicate and introduce the study to the local community we submitted a story to the region-specific "Tundra Drums" newspaper and locally owned radio stations (KYKD, KYUK). Dissemination of the results will occur after each phase of the project with guidance from our CAC. The first level of dissemination will be to the YKHC Human Studies Committee and Board. After receiving approvals, the second level of dissemination will be to the local community by submitting a story to local newspapers, locally owned radio stations, and the YKHC employee website. A booklet or brochure and a power point presentation with key project findings will be developed and approved by the YKHC. Presentations will be given to community members at local gatherings in Bethel and to YKDRH providers. The YKHC staff will also travel to the study villages to provide promotional items from the campaign, along with the brochures and DVD digital stories. They will meet with village councils to share results as feasible.

As the third level of dissemination, we will communicate the findings state-wide with our partners at the Alaska Native Tribal Health Consortium (ANTHC). The YKHC PR department will contract with businesses of their choice to develop three 30-second DVD video spots to be used in waiting areas of prenatal clinics in the Y-K Delta Region and the 15 health care regions served by the ANTHC. Information will also be included in ANTHC newsletters. The investigators and community partners will jointly present at the Alaska Native Health Research Conference held biannually with the audience comprising community members and researchers. Tangible products will be distributed such as intervention manuals and the digital stories DVD, and training will be made available elsewhere in Alaska.

A fourth level of dissemination will be to communicate the findings to national audiences. Mayo Clinic and community partners will jointly present at the Society for Research on Nicotine and Tobacco and other national scientific meetings. Also, we will communicate findings to our national AI/AN partners through our NCI funded U54 Community Networks Program grant (Kaur, PI) of which Dr. Patten is the research director.

The final level of dissemination will involve peer-reviewed publications written and co-authored with our community partner. As in prior studies, CAC members will also have the opportunity to co-author manuscripts and presentations. Utilizing these various venues for communication and dissemination of the project findings will maximize dissemination of the knowledge gained in this project. There should be lessons learned that will generalize to underserved populations as well as differences that will limit generalizability.

Check all that apply. If none apply, leave blank:

☐ This is a multisite study involving Mayo Clinic and non-Mayo Clinic sites.
When checked, describe the research procedures/activities being conducted **only** at Mayo Clinic:

☒ Mayo Clinic staff will be engaged in research activity at a non-Mayo Clinic site. *When checked, provide the location and a detailed description of the Mayo Clinic research staff involvement*.

The study will be conducted at the Yukon-Kuskokwim (Y-K) Delta Regional Hospital, Nicotine Control and Research Program, in Bethel, Alaska. The Yukon-Kuskokwim Health Corporation (YKHC) through the Indian Health Service P.L. 93-638 operates the Yukon-Kuskokwim Delta Regional Hospital. YKHC staff at the Y-K Delta Regional Hospital and Mayo Clinic staff share the workload of recruitment, conducting participant assessments in in the past conducted some of the intervention calls as a back-up to the YKHC research coordinator as well as the Native Sisters. Personnel modifications were approved by the YKHC HSC and Alaska Area and Mayo Clinic IRBs.

Mayo Clinic staff (Dr. Patten) traveled to Bethel, Alaska to train the research coordinator on the data collection and other study procedures. Ms. Hughes is a clinical trials coordinator and study assistant at Mayo Clinic. We used the same coordination, communication and quality control procedures successfully utilized in our previous work. For ongoing trials in Alaska, we hold weekly conference calls with study staff in Bethel and at Mayo Clinic to discuss progress and problem solve issues related to recruitment and data collection. We also monitor quality control of the data on site in Bethel through review of participant forms and procedures every 3 months. Mr. Paul Decker, Biostatistician on this protocol will oversee the transfer of data forms and data storage.

The Mayo Clinic study assistant trained the research coordinator on-site in Bethel on focus group and individual interview techniques and ensure the coordinator met training requirements prior to recruitment for the focus groups.

☐ This study is to establish and/or maintain an ongoing database or registry for research purposes only.

☒ The research involves contact or interaction with subjects, for example, surveys, questionnaires, observation, blood draw.

☒ The study involves audiotaping or videotaping

Data Confidentiality, HIPAA Subject Identifiers

Review the list of subject identifiers below and, if applicable, check the box next to each subject identifier being recorded at the time you are collecting/abstracting data/specimens for use in this study.

Subject Identifiers: Individually identifiable information, including demographic data, that identifies the individual or for which there is reasonable basis to believe it can be used to identify the individual. NOTE: Identifiers apply to subjects enrolled in your study and to the subject's relatives, household members, employers, etc.

Internal refers to subject identifiers that will be included in the dataset maintained by the study team.
External refers to subject identifiers that will be shared with persons outside of the immediate study team, for example, sent to an external collaborator or shared with a national registry.

SUBJECT IDENTIFIERS **Check all that apply**	INTERNAL IDENTIFIER	EXTERNAL IDENTIFIER
Name	X	
Social Security number		
Medical record/patient registration number, lab accession, specimen or radiologic image number		
Study number, subject ID, or any other unique identifying number, characteristic or code that can be used to link the identity of the subject to the data	X	
Dates: All elements of dates [month, day, and year] directly related to an individual. Their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	X	
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address	X	
Street address, city, county, precinct, zip code, and their equivalent geocodes	X	
Phone or fax numbers	X	
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
If None of the above identifiers will be recorded or maintained in the dataset and/or sent outside of the study team, please check "None".	☐ None	☒ None

Statistical Information

Note: Power analyses and study endpoints are not needed for a pilot or feasibility studies.

☐ No statistical information. *If checked, please explain*:

Statistical Considerations
Phase I:

Sampling Strategy:

We used a stratified purposeful sample with divisions based on audience segment (pregnant women, family members, Elders), gender and current tobacco use status (Table 1). We stratified by gender because we found this approach facilitates interaction and participation. Among pregnant women, we held separate groups based on whether or not tobacco was used in the 3 months before pregnancy, as different messages were created targeting prevention and cessation of tobacco, respectively. Once data saturation (no new information is being collected) was achieved, the focus groups ceased**.** Between 6-12 participants per focus group is recommended. Based on our experience, focus groups of about 8 participants are ideal for information sharing and individual participation in this region. However, it was not feasible to recruit large numbers of Elders for focus groups, it was difficult to recruit non-users, and we experience scheduling difficulties. This lead to some focus groups being less than optimal and we conducted individual interviews when needed. We estimated 8 per focus group with pregnant women (N=32) and family members (N=32), and 4 per group with Elders (N=16); for a total of 80 participants. We had 23 pregnant women, 26 family members and 11 Elders that participated in focus groups/individual interviews.

For the second round of assessments, we recruited a different sample to pre-test draft concepts of the campaign messages and media. Based on sample size recommendations for qualitative interviews, we planned to conduct a total of 50 individual interviews (20 pregnant women, 20 family members and 10 Elders), with divisions based on the subsets in Table 1. For this second assessment, we interviewed 20 pregnant women, 21family members and 11 Elders.

Data Analysis Plan:

Focus Group Qualitative Analysis. Sample characteristics were summarized using descriptive statistics. Audiotapes were fully transcribed with statements in Yupik translated locally. Focus group data were analyzed using content analysis and NVivo 10 to facilitate and streamline our analysis. Codes and categories were developed around the phenomena of interest. Initially these codes were based on the themes in our moderator guide; these themes have been refined and revised to incorporate themes that emerge from the data. In addition to open coding, planned comparisons across categories of interest were carried out (e.g., tobacco use status, gender), and connections established between identified categories. The analysis process was enhanced through memo writing and summarizing of emerging themes by the facilitators after each focus group. Focus group themes were discussed and refined with the facilitators until consensus is reached, and will be reviewed with our CAC. The analysis process was documented and outlined via the use of data management software, NVivo 10. Next qualitative findings will be synthesized with our health communications framework and relevant literature.

Individual Interviews Data Analysis: Data was analyzed using frequencies and other descriptive statistics for the overall sample. Trends within and between subgroups (e.g., pregnant women who use vs. do not use tobacco) were examined using the Chi-square (exact) or two-sample rank sum test. The investigative team synthesized the findings with our health communication framework and the literature. Results and recommendations were reviewed and finalized with our CAC, Northwest Strategies and nDigiDreams.

Phase II:

Power Statement:

Sample size calculations are based on the primary endpoint of tobacco use at 6 months postpartum. From our pilot data, of the 400 women who reported tobacco use during the 3 months prior to pregnancy, 83% reported tobacco use during the prenatal period and 69% at 6 weeks postpartum. Among the 17% of women

who quit tobacco use during pregnancy, the relapse rate was 63% at 6 weeks postpartum. Of the 432 women reporting no tobacco use in the three months before pregnancy, 75% reported tobacco use during the prenatal period, and 70% at 6 weeks postpartum. Alaska PRAMS data indicate similar cessation rated during pregnancy (20%) and rates of relapse postpartum (57%) in the southwest region. During the time periods these estimates were obtained, women received the same standard of care as in the proposed study. Therefore, we do not expect our usual care condition to impact tobacco use beyond the natural history of tobacco use in pregnancy. The Clinical Practice Guideline meta-analysis found that behavioral/psychosocial interventions for pregnant smokers were associated with an abstinence rate of 13% in late pregnancy vs. 7% for control conditions (OR= 1.8, 95% CI 1.5-2.3). We do not have guidance from the literature on the possible impact of interventions for baseline non-tobacco users but would expect greater impact in this group compared to those already using tobacco. Accordingly, we estimate the rate of tobacco use at 6 months postpartum to be 70% in our control villages and 55% in the intervention villages (estimated odds ratio 1.91) and in late pregnancy to be 80% vs. 65% with an odds ratio of 2.15. A difference of 15% would be of clinical significance in terms of the potential to impact the current standard of care at the YKDRH.

Estimates of intra-class correlations (ICC) within communities are quite modest, e.g., ranging from 0.002 to 0.012 for a variety of survey variables included in the Minnesota Heart Health Program. For the proportion currently smoking the estimated ICC was 0.00272. Other literature indicates that in community based trials using group-randomized designs (e.g., NCI Working Well Trial) the ICC ranged from 0.01-0.03 for the four outcome variables at baseline. Lumley et al. reviewed 9 cluster randomized trials of prenatal cessation interventions but most did not report the ICC and/or account for the clustering effect in the analysis. Table 3 (below) provides power estimates for the estimated outcomes with 16 villages total, average village participant size of 20 (total sample size = 320), and with varying ICC estimates. With an ICC of 0.01 we will have >80% power to detect the hypothesized differences between conditions at 6 months postpartum.

Table 3. Power estimates for 1-sided alpha=0.05 test

	Hypothesized difference in tobacco use rates	
ICC	Late Pregnancy 65 vs. 80%	6 Months Postpartum 55 vs. 70%
0	91	87
0.001	91	86
.01	86	81
.02	82	76
.03	77	71

Data Analysis Plan:

Analyses will be performed by Paul Decker, M.S. who has extensive experience in analysis of randomized clinical trials, with consultation from Dr. David Murray. Recruitment data will be summarized, including the total number of potential participants screened from each village, the number excluded for each of the specific inclusion/exclusion criteria, and the number of eligible women who agree to participate. To assess reach of the program in each village, we will calculate the proportion of subjects enrolled to total eligible subjects. We will compare the recruitment rates between control and intervention villages using the chi-square test. Potential village effects on recruitment rate will be explored.

Baseline demographics will be summarized and compared between intervention and control villages using the chi-square test for categorical variables and the two-sample t-test/rank sum test for continuous variables. The biochemically confirmed 7-day point prevalence tobacco use rate at 6 months postpartum will be summarized for each condition (point estimate and 95% CI) among participants eligible for follow-up (i.e., excluding women experiencing a miscarriage, abortion or fetal demise) and compared between conditions using generalized estimating equations (GEE) with a logit link function to account for clustering of outcomes within village (ICC) (**Aim 1**). We will utilize an intent-to-treat approach, with participants eligible but lost to follow-

up or who do not provide biochemical confirmation classified as using tobacco. The analysis will be supplemented with multiple imputation methods to classify lost to follow-up as tobacco users or non-users. GEE will also be used to examine condition differences on the point prevalence tobacco use rates at 12 weeks/ week 36 gestation, and at 8 weeks postpartum. Because only 14 df are available for the test of the intervention we will employ a small sample correction to the standard GEE. For these analyses, the stratification factor (village size) will be adjusted for in the analysis. Based on the biochemically confirmed tobacco use status at baseline, in an exploratory fashion we will examine potential treatment effects separately among baseline non-tobacco users and tobacco users respectively using GEE. Within intervention villages only, exposure dose will be tested as a predictor of tobacco use at 36 weeks gestation and 6 months postpartum using GEE. A similar analysis will be performed using the intervention implementation index to examine potential dose response effects. Assuming an ICC of 0.01 and an effective sample size of 135 subjects in the intervention arm after correction for the ICC, there will be 80% power to detect an effect size of at least 0.5 standard deviation units when examining the association of intervention exposure (i.e., continuous measure) and abstinence rates. Potential village differences on intervention exposure or implementation will be summarized graphically and compared using GEE. The percentage of enrolled participants who complete 6- month follow-up postpartum (retention) will be compared between intervention and control villages using GEE.

We will follow procedures suggested by MacKinnon to assess mediation (**Aim 2**), fitting three GEE models to the data. We will first estimate the intervention effect separately for the dependent variable (with regression adjustment for covariates). That model provides an estimate of the total effect of the intervention, which MacKinnon labels C. Next we will estimate the intervention effect for each mediator (with regression adjustment for covariates); that model provides an estimate of the effect of the intervention on the mediator, which MacKinnon labels A. Finally we will estimate the mediated intervention effect for the dependent variable by adjusting for the mediator (and covariates); that model provides an estimate of the unmediated (i.e., direct) intervention effect, which MacKinnon labels C, and the intervention-adjusted effect of the mediator on the dependent variable, which MacKinnon labels B. Assuming an ICC of 0.01 and an effective sample size of 270 subjects after correction for the ICC, there will be 80% power to detect an effect size of at least 0.35 standard deviation units for paths A and B assuming a two-sided, alpha=0.05 test at 6-months postpartum.

Treatment condition differences on changes in other variables targeted (see Table 4) will be examined using GEE with a logit (binomial outcome) or identify (continuous outcome) links as appropriate.

We will summarize the cost of the program per pregnant woman enrolled (reached) along with cost per woman abstinent from tobacco at 6 months postpartum follow-up using descriptive statistics.

Endpoints

Primary:

Biochemically confirmed tobacco abstinence at 6-months post-partum.

Secondary:

Biochemically confirmed tobacco abstinence at end of pregnancy. Also, changes in proposed theory-based mediators of intervention efficacy.

Project Timeline

We have received approval from NIH to extend out the study timeline from 5 to 6 years total. We are currently beginning the 5th year of our 6-year NIH grant. Table 4 shows the timeline for the remaining Phase II

activities. We will request from NIH a 7th project year as a no-cost extension to complete analyses and dissemination if necessary and long as remaining funds permit.

Table 4

PROJECT TIMELINE, YEARS 3-7,
Dates: May 1, 2015 – April 30, 2020

	Year 3 2015-2016				Year 4 2016-2017				Year 5 2017-2018				Year 6 2018-2019				Year 7 2019-2020 No Cost Extension			
Month: **Activity**	1-3 May -Jul	4-6 Aug -Oct	7-9 Nov -Jan	10-12 Feb -Apr	37-39 May -Jul	40-42 Aug -Oct	43-45 Nov -Jan	46-48 Feb -Apr	13-15 May -Jul	16-18 Aug -Oct	19-21 Nov -Jan	22-24 Feb -Apr	25-27 May -Jul	28-30 Aug -Oct	31-33 Nov -Jan	34-36 Feb -Apr	37-39 May -Jul	40-42 Aug -Oct	43-45 Nov -Jan	46-48 Feb -Apr
Phase I																				
Manuscripts/scientific presentations of results; tribal approval						X														
Phase 1 results submitted to journal							X	X												
Phase II																				
Hire and train Native Sisters		X	X	X																
~~IRB~~/Tribal submission of Phase 2 working protocol	X	X																		
Train Health Aides in study villages			X	X																
Mass produce media/materials after tribal approvals		X																		
Recruitment				X	X	X	X	X	X	X	X	X								
Intervention delivery				X	X	X	X	X	X	X	X	X	X	X	X					
Follow-up					X	X	X	X	X	X	X	X	X	X	X	X				
Analysis								X					X	X	X	X	X	X	X	
Scientific and community dissemination (Phase II)																			X	X