

ZEN Colombia Study
Zika in Pregnant Women and Children in Colombia

Supporting Statement: Part A

Submitted: September 26, 2016
Revised: October 21, 2016

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Goal of the study: The goal of the ZEN Colombia study is to better understand modifiable factors affecting the acquisition of Zika infection among pregnant women in Colombia, and the link between infection and adverse outcomes following Zika infection during pregnancy.

Intended use: The data from the ZEN Colombia study will provide critical information leading to evidence-based strategies to prevent ZIKV infection in pregnancy; improved counseling of patients about risks to themselves, their pregnancies, and their children; and effective preparedness for agencies providing services to affected children and families.

Methods to collect: The proposed information collection is for a prospective cohort study following pregnant women enrolled in the first trimester, their male partners, and their infants at several sites in Colombia. This study will use paper questionnaires administered at study enrollment and follow-up visits for pregnant women from first trimester until infant follow-up at 6 months of age. Paper questionnaires for male partners will be administered at the time of enrollment and monthly intervals until the end of the second trimester of pregnancy. Study staff will abstract medical records from mothers' prenatal care, sick visits, and delivery to capture relevant medical information and from infants' medical records to obtain information on diagnoses, test results, medical procedures, and hospitalizations up to the 6 month birthday.

How data will be analyzed: A variety of methods will be used to analyze the data from the ZEN Colombia study. These methods include: descriptive analysis, log-binomial regression, Kaplan-Meier survival analysis and multivariable Cox regression, and Wilcoxon rank sum tests. These methods will be used to address the specific research questions described in Section.A2 (below).

Overview

A causal link has been established between Zika virus (ZIKV) infection in pregnancy and microcephaly and other severe fetal brain defects. CDC surveillance and research efforts are underway in the United States (U.S.) (including territories, particularly Puerto Rico), Brazil, and Colombia to understand the range of other adverse pregnancy and infant outcomes associated with Zika infection during pregnancy. However, there are key knowledge gaps that cannot be addressed using surveillance data or retrospective data, and thus there is an urgent need to prospectively study pregnant women in areas of high Zika virus transmission in order to contribute to understanding of:

- Risk factors for ZIKV infection in pregnant women and their infants, including behaviors such as use of mosquito-bite prevention measures or condoms to prevent sexual transmission, and factors associated with maternal-to-child transmission;
- Absolute and relative risk for adverse maternal, fetal, and infant outcomes associated with ZIKV infection; and
- Modifiers of the risk for adverse outcomes among pregnant women and their infants following ZIKV infection, including gestational age at infection, presence of ZIKV symptoms, extended viremia, mode of transmission, prior infections or immunizations, and co-infections.

In early February 2016, President Obama and Colombia's President Santos met and agreed that the U.S. and Colombia would conduct joint epidemiologic investigations through Colombia's Instituto Nacional de Salud (INS) and the U.S. Centers for Disease Control and Prevention (CDC). These joint research efforts include estimating the prevalence of microcephaly in Colombia, assessing risk factors associated with Zika virus infections and microcephaly, and to better understand the (at that time) potential link between Zika infection and adverse birth outcomes. Please see: <https://www.whitehouse.gov/the-press-office/2016/02/04/fact-sheet-peace-colombia-new-era-partnership-between-united-states-and> for additional details. Following this meeting, CDC received a formal letter of invitation from the Vice Minister of Health of Colombia requesting technical assistance and collaboration regarding the Zika virus epidemic (available upon request). Multiple projects have been jointly developed between INS and CDC, including enhanced surveillance of pregnant women with symptomatic Zika virus disease. We now seek to implement a prospective cohort study in which we will follow women enrolled in the first trimester of pregnancy, their male partners, and their infants in several cities in Colombia in which ZIKV transmission is currently ongoing.

CDC seeks expedited OMB approval to conduct information collection for three years, for the ZEN Colombia study. This information collection request describes the study plan, data collection instruments, and estimated total burden hours and government cost. The findings of this investigation is imperative as the information has the potential to affect CDC's recommendations and guidelines surrounding prevention of ZIKV infection in pregnancy and infancy both internationally and domestically.

A. Justification

A.1. Circumstances Making the Collection of Information Necessary

ZIKV is a mosquito-borne flavivirus transmitted by *Aedes* species mosquitoes; sexual transmission, mother-to-child transmission, and laboratory-acquired infections have also been reported. Evidence of human ZIKV infection was observed sporadically in Africa and Asia prior to 2007, when an outbreak of ZIKV caused an estimated 5,000 infections in the State of Yap, Federated States of Micronesia. Since then, evidence of ZIKV has been found in 65 countries and territories, mostly in Central and South America. Common symptoms of ZIKV in humans include rash, fever, arthralgia, and nonpurulent conjunctivitis. The illness is usually mild and self-limited, with symptoms lasting for several days to a week; however, based on previous outbreaks, some infections are asymptomatic. The prevalence of asymptomatic infection in the current Central and South American epidemic is unknown.

Although the clinical presentation of ZIKV infection is typically mild, ZIKV infection in pregnancy can cause microcephaly and related brain abnormalities when fetuses are exposed *in utero*. Other adverse pregnancy outcomes related to ZIKV infection remain under study, and include pregnancy loss, other major birth defects, arthrogryposis, eye abnormalities, and neurologic abnormalities.

Colombia's Instituto Nacional de Salud (INS) began surveillance for ZIKV in 2015, reporting the first autochthonous transmission in October 2015 in the north of the country. As of August 2016, Colombia has reported over 102,000 suspected ZIKV cases, over 18,000 of them among pregnant women. The ZEN (Zika en Embarazadas y Niños en Colombia) Colombia study, this translates to Zika in Pregnant Women and Children in Colombia, is a prospective cohort study following pregnant women, their male partners, and their infants in Colombia. Given that the Zika virus may transition from outbreak levels to endemic level, it is critical to begin enrollment rapidly to ensure that a large number of pregnant women with Zika virus infection in the first trimester can be enrolled and followed up to assess outcomes.

This study supports CDC's mission as authorized in section 301 of the Public Health Service Act (42 U.S.C. 241) (Att A).

A.2. Purpose and Use of Information Collection

CDC's goal in developing the ZEN Colombia study is to better understand the adverse pregnancy, maternal and infant health outcomes associated with ZIKV during pregnancy and/or early infancy. In addition, the ZEN Colombia study will assess the modifiable factors affecting the acquisition of Zika infection among pregnant women in Colombia. The data from the ZEN Colombia study will provide critical information supporting the evidence-based strategies to prevent ZIKV infection in pregnancy; improved counseling of pregnant women and their partners about risks to themselves, their pregnancies, and their children; and effective

preparedness for agencies providing services to affected children and families.

The primary research questions we aim to address with the ZEN Colombia study are:

1. Evaluate associations between ZIKV in pregnancy and adverse pregnancy or maternal outcomes, such as preterm birth, preeclampsia, maternal death, postpartum hemorrhage, and intrapartum fetal demise, among others. Effect modification by gestational age of infection will also be explored.
2. Quantify the magnitude of the association between ZIKV infection in pregnancy and major birth defects, with specific focus on microcephaly and congenital Zika syndrome. The prospective design of the study will allow estimation of both absolute and relative risk for microcephaly for women with ZIKV infection during pregnancy.
3. Identify risk factors for symptomatic ZIKV infection in pregnancy among all women with laboratory-confirmed ZIKV in pregnancy. A spectrum of risk factors will be considered, including maternal demographics, ZIKV infection characteristics, and other potential risk factors such as smoking and medication use.
4. Identify risk factors for ZIKV infection in infancy. A spectrum of risk factors will be explored, including maternal infection factors and birth and pregnancy factors.
5. Identify risk factors for symptomatic ZIKV infection in infancy among infants with laboratory-confirmed ZIKV born to women enrolled in the study. A spectrum of risk factors will be considered, including maternal ZIKV infection in pregnancy factors, co-infections, sociodemographic characteristics and birth factors.
6. Investigate associations between ZIKV infection in utero or in infancy and hearing loss and other physical, neurologic, and neurodevelopmental outcomes at 6 months of age.
7. Estimate survival of infants born to ZIKV infected mothers.

Secondary research questions we aim to address with the ZEN Colombia study are:

1. Identify risk factors for ZIKV infection in pregnant women, partners and infants. A spectrum of risk factors will be explored, including mosquito bites and mosquito bite preventive measures, sexual transmission, sociodemographic characteristics, and medical risk factors. The results of this analysis will provide information on the reduction in risk associated with adherence to recommended preventive measures and risk factors for infection in pregnant women.
2. Identify characteristics associated with taking preventive measures (mosquito bite prevention, sexual transmission) against contracting Zika virus among pregnant women and their partners. The results of this analysis will assist in targeting education or intervention to individuals at greatest risk for Zika infection.
3. Describe symptoms associated with ZIKV and estimate the positive predictive value of certain symptoms or constellations of symptoms in pregnant women, men, and infants to allow for refinement of clinical diagnosis of ZIKV infection in a setting in which testing and/or results might not be readily available.
4. Assess the duration of viremia following ZIKV infection and investigate risk factors (such as sociodemographics, comorbidities, and co-infections) associated with prolonged viremia among pregnant women, men, and infants with laboratory-confirmed ZIKV infection in blood.

This study is a part of an ongoing public health emergency response related to the Zika virus outbreak in Colombia. Results of this study will be used to guide INS's and CDC's recommendations for surrounding prevention of ZIKV infection in pregnancy and infancy both internationally and domestically; to improve counseling of patients about risks to themselves, their pregnancies, their partners, and their children; and for enhancing preparedness of agencies providing services to affected children and families.

A.3. Uses of Improved Information Technology and Burden Reduction

The ZEN Colombia study questionnaires have been designed to collect the minimum amount of information necessary to meet the study's objectives. Questions about other factors with the potential to have mediating or moderating effects on primary outcomes have been considered and included. All questionnaire data will be obtained in person with participants via paper forms. All data will be entered and stored on the password-protected and secure web-based data collection system which will be housed on an INS server in Colombia.

A.4. Efforts to Identify Duplication and Use of Similar Information

While many experts agree that ZIKV causes microcephaly, more studies are needed to better understand the full spectrum of defects and other adverse pregnancy and infant outcomes caused by congenital ZIKV infection, to quantify the relative and absolute risks of these outcomes among infants who are born to women who were infected at different times during pregnancy, and to identify factors that modify the risk of an adverse pregnancy or birth outcomes (see Rasmussen et al., *N Engl J Med* 2016; 374:1981-1987). There is an urgent need to prospectively study pregnant women in areas of high Zika virus transmission because many of these key knowledge gaps cannot be addressed using surveillance data or retrospective data. Through its prospective design, the ZEN Colombia study is designed to systematically identify the timing of symptomatic and asymptomatic infections in pregnant women, the latter of which cannot be ascertained from surveillance data or retrospective studies. The prospective design also allows estimation of absolute risk of adverse outcomes, including less severe outcomes that may not yet have been identified, in addition to relative risk, because the base population is well-defined. The ZEN Colombia study is the only data source that collects comprehensive information of ZIKV infection initiating in the first trimester and associated birth defects from multiple sites in Colombia.

As part of its Zika response efforts, CDC is collaborating with the National Institute of Health (INS) in Colombia, which has had the second-most cases of the mosquito-borne Zika virus after Brazil. The large number of cases and stage of the outbreak in Colombia provides an opportunity to collect actionable information on a shorter timeframe than is possible elsewhere. This

collaboration is expected to provide critical scientific information to help the United States, Colombia, and other countries prepare for the unprecedented challenges posed by Zika. Participant enrollment is timed to coincide with the expected second wave of Zika virus cases in Colombia, the peak time for infection, and will provide CDC with the ability to rapidly obtain answers to questions about Zika that will help to shape the course of this public health emergency response.

Although the National Institutes of Health (NIH) developed an international effort to conduct a multi-country cohort study to evaluate risk of ZIKV infection among pregnant women and their fetus and infants, NIH does not collect symptom information or specimens from associated male partners. The ZEN Colombia study aims to assess the relative contribution of sexual transmission and mosquito-borne transmission to occurrence of infections in pregnancy. In addition, Zika outbreak dynamics may vary according to location. While the NIH study is an international collaboration, ZEN is an intensive, prospective data collection effort focused specifically on Colombia. ZEN will address questions specified by the Colombian government, which the US government has committed to helping INS address, as specified in the agreement between Presidents Obama and Santos, as described above.

Information collection as part of this study are not conducted else within CDC or within the Department of Health and Human Services.

In general, the ZEN project is the only prospective cohort study of pregnant women currently being undertaken by CDC. Although surveillance efforts focused on ZIKV in pregnancy are currently underway in the U.S. (including territories) and Colombia, the ZEN project is the only CDC-based project that will allow

- Study of both symptomatic and asymptomatic pregnant women with ZIKV infection; and
- Estimation of the absolute risk of microcephaly and other adverse outcomes among pregnant women infected with Zika virus during different gestational ages, which is not possible using a case-control design

Ongoing projects in the CDC Zika response and how the ZEN study fill gaps not addressed by these existing efforts

Project	Contribution added by ZEN
Persistence of Zika virus in semen and urine of adult men in the United States with confirmed Zika virus infection (OMB Control No. 0920-1139)	Study population includes only adult men with Zika virus infection; one objective of ZEN includes examining persistent viremia specifically in pregnant women
Zika virus persistence in body fluids of patients with Zika virus infection in Puerto Rico (ZIPER Study) (0920-1140)	Study population includes all ages and sexes; one objective of ZEN includes examining persistent viremia specifically in pregnant women
The Effect of Community-Wide Vector Control Initiatives on Zika Virus	Not applicable – ZEN does not address community-wide vector control

Transmission in Puerto Rico, 2016 (0920-1137)	
Evaluation of In2Care Traps during the Zika Outbreak in Puerto Rico (0920-1071)	Not applicable – ZEN does not address community-wide vector control
Knowledge, Attitudes, and Practices related to a Domestic Readiness Initiative on Zika Virus Disease (0920-1136)	Not applicable – ZEN does not address a specific domestic readiness objective
Integrated Aedes aegypti Vector Control Intervention in Caguas City, Puerto Rico to Prevent and Control Zika Virus Infections (PRA N/A)	Not applicable – ZEN does not address community-wide vector control
Migrant Farm Workers Understanding and Use of Measures to Prevent Zika Transmission (0920-1126)	Not applicable – ZEN does not address migrant farm workers
US Zika Pregnancy Registry (0920-1101; new ICR under review)	This project focuses on U.S. pregnant women with laboratory evidence of Zika virus infection; Voluntary reporting to the registry may result in ascertainment bias, while ZEN will prospectively identify pregnant women in early pregnancy. In addition, the ZEN study includes collection of data from maternal questionnaires.
Assessment of Interventions Intended to Protect Pregnant Women in Puerto Rico from Zika virus infections (0920-1118)	Not applicable – ZEN does not assess the effectiveness of specific interventions in preventing Zika virus infection
Assessment of Contraceptive Use and Needs, Puerto Rico, 2016 (0920-1114)	Not applicable – ZEN does not assess contraceptive use and needs
Enhanced Surveillance of Pregnancy and Infant Outcomes following with Zika Virus infection in Pregnancy, Colombia (PRA N/A)	ZEN will prospectively identify pregnant women in early pregnancy and collect data from maternal questionnaires, rather than relying solely on medical records, as is done in this surveillance effort; the surveillance data do not allow identification of absolute risk, because the base population is challenging to quantify. Further, because infections are identified retrospectively, exact timing of infection during pregnancy cannot be ascertained. Only symptomatic pregnant women are included in the surveillance project, while ZEN will allow identification of both symptomatic and asymptomatic pregnant women.
Characterization of Guillain-Barré Syndrome Cases in the Setting of Zika	ZEN does not focus on Guillain-Barré Syndrome as an outcome

Virus Transmission— Colombia, 2016 (PRA N/A)	
Formative Evaluation of Zika Prevention Kits for Pregnant Women in Puerto Rico (0920-1071)	ZEN does not propose evaluation of Zika Prevention Kits
Case-control microcephaly study in Brazil (0920-1011)	ZEN will start with a defined base population of pregnant women at risk for Zika infection in their first trimester of pregnancy and prospectively identify timing of infection in this cohort of pregnant women, which will allow estimation of the absolute risk of microcephaly and other adverse outcomes. Retrospective case identification is vulnerable to selection bias, particularly in relation to symptomatic infection. Further, a case-control study can only estimate relative risk.
Collection of serum and plasma from patients with antibodies reactive with Zika virus and other arboviruses (PRA N/A)	ZEN focuses specifically on pregnant women and their infants
Mosquito Surveillance Survey (0920-1101)	Not applicable – ZEN does not propose to assess mosquito populations
American Samoa Zika Surveillance (0920-1011)	ZEN will prospectively identify pregnant women in early pregnancy and collect data from maternal questionnaires, rather than relying solely on medical records, as is done in this surveillance effort; the surveillance data do not allow identification of absolute risk, because the base population is challenging to quantify. Further, because infections are identified retrospectively, exact timing of infection during pregnancy cannot be ascertained. ZEN will allow identification of both symptomatic and asymptomatic pregnant women.
Case-control GBS study in PR – Surveillance (0920-1106)	ZEN does not focus on Guillain-Barré Syndrome as an outcome
Case-control GBS study in PR - Records Abstraction (PRA N/A)	ZEN does not focus on Guillain-Barré Syndrome as an outcome
Formative evaluation among partners of pregnant women about Zika in PR (0920-0572)	Not applicable – ZEN does not include formative evaluation of any programs

A.5. Impact on Small Businesses or Other Small Entities

Data will be collected from private and public health care systems in the study cities in Colombia, including some that may be small businesses. The study data collection elements are the absolute minimum required for the intended use of the data. The survey instruments will be presented in a clear and easy to complete format based on previous surveys and recommendations from survey methodology research.

A.6. Consequences of Collecting the Information Less Frequently

Each woman will participate starting in the first trimester of her pregnancy through the first 6 months of her baby's life. Each male partner will participate only during his partner's pregnancy, until about 27 weeks of gestation. Infants will participate for the first 6 months of life. It is important to monitor health status for both mothers and infants throughout pregnancy and during early infancy with multiple visits, particularly for mothers with ZIKV infection. Male partners will be monitored to ZIKV. The data collection frequency is essential to answer questions about transmission of ZIKV, adverse maternal, fetal, and infant outcomes following ZIKV infection in pregnancy, and risk factors for infection and adverse outcomes. Collecting information less frequently may not permit this determination.

A.7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

This information collection fully complies with all guidelines of 5 CFR 1320.5.

A.8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

No public comments are required because this investigation is a part of an ongoing public health emergency response related to the Zika virus outbreak in Colombia.

CDC has consulted with other public health agencies, e.g., NIH, to ensure there are no duplication of similar efforts in the study location.

A.9. Explanation of Any Payment or Gift to Respondents

Participants will be provided with a per diem that was designed to defer the outlay of expenses incurred by any adult participants for travel and meals associated with study clinic visits. In accordance with Colombian guidelines, this value has been determined based on the local economy and research studies conducted in this population. The intent of the per diem is to minimize personal financial outlay of participants for their time and travel.

Participants will be provided with per diem for each clinic visit that is requested as part of the ZEN protocol. While ZEN clinic visits were designed to largely align with Colombian standard of care for prenatal or infant well-being visits, full compliance with prenatal and infant standard of care visit schedules may not always occur due to resource and access to care barriers. To improve quality of the overall data collected, ZEN study staff will facilitate access to all visits as discussed in the protocol. To do so, ZEN will need to remove resource barriers to accessing care, making it appropriate for the study to provide per diem for clinic visits.

When a participant attends a scheduled clinic visit, he or she will receive 20,000 Colombian pesos (about 7 USD) for travel costs. The cost of public transportation to the city costs between approximately 12,000 to 20,000 pesos per round trip, depending how far the participant lives from the clinic. If the time spent at the study visit extends through lunch, then the participant may be provided costs to cover a meal, 10,000-12,000 pesos (about 3 USD). These may be given to the participants in the form of cash or transportation tickets.

A. 10. Assurance of Confidentiality Provided to Respondents

Data will be collected as information in identifiable form (IIF) therefore the Privacy Act does apply. The compilation of individual research results and responses into a study database for the ZEN Colombia study will be used only for research purposes. Investigators have completed certifications in Information Security and Privacy Awareness and will put systems in place to meet Privacy Act requirements. The sections below describe the protections in place to preserve privacy and confidentiality.

A. 10.1 Overview of the Data Collection System

Pregnant women will be recruited in the first trimester of pregnancy at participating clinics in Colombia's private and public health care systems and followed through their pregnancy, delivery, and immediate post-partum period. The Pregnant Woman Eligibility Screener Form (Att B.1), administered to potential participants by trained ZEN research staff, will be used to confirm participant eligibility prior to consent. At the enrollment visit, pregnant women will be given the Pregnant Woman Enrollment Questionnaire (Att B.2) which includes information on demographics, risk factors for Zika virus exposure, pregnancy and medical history, and risk factors for ZIKV exposure and an Adult Symptoms Questionnaire (Att B.5). All pregnant women will attend monthly study visits that coincide with their prenatal care visits through the end of pregnancy and will be given the Maternal Follow-Up (Att B.3) and Adult Symptoms Questionnaires (Att B.5). Pregnant women will be monitored for incident ZIKV infection by collection of urine, about two weeks after visits to the clinic, until the middle of the third trimester (approximately 32 weeks gestation). If a woman is confirmed to have ZIKV, she will complete an Adult Symptoms Questionnaire (Att B.5) every 2 weeks until she is negative for 2 consecutive samples. If a woman chooses to terminate a pregnancy or has a spontaneous fetal demise, an Adult Symptoms Questionnaire (Att B.5) will be administered at that time. At delivery or within 72 hours postpartum, the mother will be administered the Infant Symptoms

(Att B.6), Adult Symptoms (Att B.5), and Maternal Follow-Up (Att B.3) Questionnaires.

Infants of mothers participating in the study will be followed from birth to 6 months of age to detect health outcomes that might not have been detectable at birth. Study visits will correspond to regular well-baby visits at 1, 2, 3 and 6 months of age. Study staff will conduct developmental assessments, physical examination, and hearing and eye exams. Mothers will be administered the Infant Symptoms Questionnaire (Att B.6) at each visit. Urine samples will be collected every 2 weeks to monitor for incident ZIKV infection in infancy. If an infant is confirmed to have ZIKV, the mother will administered the Infant Symptoms Questionnaire (Att B.6).

In addition to administered questionnaires, ZEN Colombia study staff will abstract medical records from mothers' prenatal care, sick visits, and delivery to capture relevant medical information. Mothers' medical record abstraction will be conducted up to 6 months after delivery to collect information on post-partum medical issues. Staff will also abstract medical records from children enrolled in the study to obtain information on diagnoses, test results, medical procedures, and hospitalizations up to the 6 month birthday.

Male partners will be recruited via their pregnant partners around the time of their partners' enrollment into the study. The Male Partner Eligibility Screener Form (Att B.8), administered to potential participants by trained ZEN research staff, will be used to confirm participant eligibility prior to consent. At enrollment, men will provide a blood sample and complete the Male Enrollment Questionnaire (Att B.4) and Adult Symptoms Questionnaire (Att B.5). Men will provide urine samples monthly through the second trimester of their partner's pregnancy (about 27 weeks of gestation) to monitor for incident ZIKV infection. Men will complete the Adult Symptoms Questionnaire (Att B.5) at the time of each specimen collection. If the male partner is confirmed to have ZIKV, semen collection kits will be provided to the participants with instructions for home collection. Semen will be collected every 2 weeks until semen is negative for ZIKV for two consecutive samples or until the partner's pregnancy ends. Semen samples will be picked-up by study staff when they are conducting their home visits. If a man does not want to provide semen samples, follow-up will be discontinued.

A. 10.2 Description of Information to be Collected

Data collection includes maternal demographic information, pregnancy history, medical history, Zika virus infection, and pregnancy outcome information (including infant anomalies and birth defects). The follow-up questionnaire update information from the previous study visit including behavioral, sexual, environmental, or other risk factors for ZIKV or adverse pregnancy outcomes. ZIKV symptoms questionnaires assess symptoms and dates of symptom onset among study participants or their household contacts.

A. 10.3 How Information Will Be Shared and for What Purpose

There are three main entities involved in the conduct of the ZEN Colombia study. Colombia's Instituto Nacional de Salud (INS) is CDC's scientific collaborator on this study. CDC employs a contractor, Vysnova Partners, Inc., to conduct the ZEN Colombia study in collaboration with INS. All CDC, INS, and contractor personnel who have access to protected data are required to go through training on confidentiality protections and to sign a nondisclosure agreement (Atts D.1, D.2, D.3).

Patients' personally identifiable information (PII) will not be disclosed in any reports, statistical summaries, or shared or disclosed to public entities, external agencies, or other people or organizations outside the entities involved in the conduct of the ZEN Colombia study. We have engaged in discussions with researchers at the National Institute of Health who are launching the ZIP pregnancy cohort in several countries, including Colombia and the Center for Global Health at CDC who will be providing technical assistance to several smaller pregnancy cohorts in Guatemala, Kenya, Thailand and Haiti. Globally, there is an interest in some degree of harmonization across these studies, to ultimately be able to conduct meta-analyses, or at a minimum, compare results. If there is any possibility of sharing of de-identified data with selected researchers such as those noted here, we will certainly engage INS in any decision to do so. Currently, our plan is to definitely share statistical summaries of de-identified data in peer-reviewed journals and conference presentations.

A. 10.4 Impact on the Respondent's Privacy

ZEN study site staff will protect the confidentiality of participant data and research records by assigning a unique study Participant Identification Number (PIN) to all study forms, specimens, and database. To ensure the anonymity of the research data, this PIN will be the only identifier associated with a subject's research data, such as their questionnaire responses, laboratory results, and abstracted medical information. An electronic crosswalk file that is separate from the research data will be kept to provide the link between the unique subject PIN and associated PII (e.g. names, dates of birth, contact information, etc.). Resulting reports or publications regarding this research are to be reported in aggregate and ensure individuals cannot be identified. A number of procedures and security measures are in place to protect patient privacy. At clinical sites, study forms will be stored in a locked file cabinet that only study staff can access. Study data will be stored on a password-protected database that only study staff can access. Patients' personally identifiable information (PII) will not be shared or disclosed to public entities, external agencies, or other people or organizations outside the entities conducting the ZEN Colombia study. CDC's Institutional Review Board oversees certain types of data analysis conducted with this information collection, and the confidentiality of information submitted by patients and clinics is protected by an Assurance of Confidentiality under Section 308(d) of the Public Health Service Act. CDC has an Assurance of Confidentiality for this study. INS employees are not covered by this Assurance of Confidentiality.

A. 10.5 Explaining Voluntary Nature of Participation

During the administration of the informed consent document, ZEN study staff will explain to respondents that participation is voluntary, they can end their participation at any time without negative consequences. An informed consent for the collection of data has been approved (Atts B.7 and B.9).

A. 10.6 Opportunities to Consent to Sharing and Submission of Information

The informed consent document (Att D.7) clearly explains that the study findings will be compiled and only presented on a group level, with no individuals identified. Participants are also told that relevant test results will be shared with their doctors. In addition, within the informed consent document, there is a separate item where the participant must check “Yes” or “No” regarding their approval to allow researchers store study samples and health information for future research.

A. 10.7 How Information Will Be Secured

Paper documentation, such as the Questionnaires and documentation of informed consent, will be stored in a designated and secured office area and similarly designated and locked filing cabinet within each study site. Research data store in on online database (RedCap) will be kept secure and confidential on the INS server, which will require user authentication and password protection. Administrator controls in place include regular backups, security training, completion of a security certification and accreditation (C&A), security plans, and policies. Access to ZEN Colombia study data is limited to CDC, INS, and contractor staff supporting the project. The contractor follows federal security requirements and adheres to all CDC security policies and regulations. Requirements for adherence to privacy provisions and policies, as well as instructions for destruction of study data and files when the contract ends, are specified in the contract language.

A. 11. Institutional Review Board (IRB) and Justification for Sensitive Questions

The CDC Institutional Review Board (IRB) approved the study as research (Att C.1). The protocol was reviewed in accordance with the expedited review process outlined in 45 CFR 46.110(b)(1), Categories 2, 5, and 7. The IRB determined the study to be not greater than minimal risk to subjects. The IRB approved the inclusion of children under 45 CFR 46.404 and the inclusion of pregnant women under 45 CFR 46.204.

IRB approvals from INS and Vysnova Partners, Inc, are pending. The study will not commence until all IRB approvals are obtained.

The participating IRBs will also conduct continuing reviews of routine annual data points as

well as required review of any adverse events or protocol violations as needed. Some data to be collected for ZEN Colombia may be sensitive in nature to some respondents. To reduce the sensitivity of these questions, respondents will be completing questionnaires in private and will be reminded that they are not required to answer any questions to which they would prefer not to respond. Topics that may be perceived by subjects as sensitive are: 1) patient demographic information including social-economic status; 2) patient medical history including number of pregnancies lost; 3) ZIKA knowledge, symptom and diagnosis information; 4) sexual behavior and practice, and alcohol or drug use; 5) pregnancy outcome information; and 6) infant health information.

CDC developed the data collection requirements after extensive consultation with medical professionals and epidemiologists. There is consensus that the sensitive information collected is necessary to provide accurate information of the ZIKV infection in order to identify associated risk factors and adverse maternal, fetal, and infant adverse outcomes following ZIKV infection in pregnancy.

A. 12. Estimates of Annualized Burden Hours and Costs

Burden Hours

Respondents are pregnant women and their male partners who agree to participate in the study.

ZEN Colombia study staff will use the Eligibility Screener Questionnaire to confirm eligibility of pregnant women. Because it is administered prior to initiation of the consent process, the burden estimate for administration of the ZEN Screener Questionnaire is based on a larger pool of pregnant women than that of women eligible and consented for the ZEN study. This assumes 25% of women screened will not meet eligibility criteria. The remainder of the burden estimate is based on completion of questionnaires by consented respondents: 5,000 pregnant women, 1,250 male partners, 5,000 fetuses, and 4,500 newborns. This assumes a 25% participation rate among male partners and that 90% of infants are live born.

As exhibited in Table A.12-1, each study questionnaire instrument is considered one response. The annualized burden hours for each questionnaire was calculated by multiplying the number of respondents by the number of responses (estimated number of times each questionnaire would be completed) per respondent by the average burden per response. The total estimated annualized burden for all information collection for ZEN is 25,665 hours.

A. 12 – 1 Estimated Annualized Burden Hours

Respondent	Form Name	No. of	No. of	Average	Total
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s		Respondent s	Responses (Questionnaires) per Respondent	Burden per Response (in hours)	Burden Hours
Pregnant women	Pregnant women eligibility questionnaire	6,250	1	5/60	520
	Pregnant women enrollment questionnaire	5,000	1	20/60	1,666
	Adult symptom questionnaire	5,000	12	5/60	5,000
	Pregnant women follow-up questionnaire	5,000	12	15/60	15,000
	Infant symptoms questionnaire	4,500	4	5/60	1,500
Male partners	Male partner eligibility questionnaire	5,000	1	5/60	417
	Male enrollment questionnaire	1,250	1	15/60	312
	Adult symptom questionnaire	1,250	12	5/60	1,250
				Total	25,665

a) Estimated Annualized Cost to the Federal Government

Information for the ZEN Colombia study is collected by nurses, data entry clerk, field study staff, lab technicians, and physicians.

A. 12 – 2 Annualized Cost to Respondents

Type of Respondent s	Form Name	Number of Respondent s	Number of Responses per Respondent	Average Burden Hours per Response	Total Burden Hours	Hourly Wage Rate	Total Costs
Pregnant women	Pregnant women enrollment questionnaire	5,000	1	20/60	1,666		
	Adult	5,000	12	5/60	5,000		

	symptom questionnaire						
	Pregnant women follow-up questionnaire	5,000	12	15/60	15,000		
	Infant symptoms questionnaire	4,500	4	5/60	1,500		
Male partners	Male enrollment questionnaire	1,250	1	15/60	312		
	Adult symptom questionnaire	1,250	12	5/60	1,250		
Total							

A. 13. Estimates of Other Total Annual Cost Burden to Respondents or Record Keepers

There are no additional costs to respondents other than their time

A. 14. Annualized Cost to the Federal Government

Estimates of annualized costs to the federal government are included in the following table.

A. 14 – 1 Annualized Cost to the Federal Government	
ZEN Colombia Study	
Contract	Annualized Cost
1. Total labor	\$1,842,321.00
2. Total other direct costs	\$1,224,408.00
3. Total overhead	\$11,203.50

4. General and administrative expense	\$279,177.00
5. Fee @ 8%	\$107,269.00
Subtotal	\$3,464,318.50
CDC FTEs	Salary
1. Epidemiologist, GS-601-14/15	\$228,500
2. Epidemiologist, GS-601-13	\$160,000
3. Health Scientist, GS-601-13	\$117,660
4. Statistician, GS-1529-13	\$67,500
5. Public Health Analyst, GS-1529-13	\$67,500
Subtotal	\$641,160
Total Federal Government Cost	\$4,105,478.50

The annualized cost to the federal government is \$4,105,478.50, which includes the contract with Vysnova and CDC staff time to oversee and collaborate on the study. The annual cost of the contract with Vysnova is \$3,464,318.50, which includes operational costs, contractor personnel, facilities, equipment, supplies, laboratory diagnostic tests, and materials necessary to assist CDC with the ZEN Colombia study. CDC staff members provide technical oversight and expertise, including analytic and scientific guidance, on ZEN and to the contract staff. CDC staff members participate in reviewing study protocol, implementation, and attend site visits. CDC staff also conducts scheduled calls to monitor the contractor’s performance and ensure that project standards are met and that the data are of high quality, thus ensuring accurate reporting and generation of valid success rates. CDC staff listed in table A.14-1 dedicates approximately 100% of their time to these activities.

A. 15. Explanation for Program Changes or Adjustments

This is a new collection of information.

A. 16. Plans for Tabulation and Publication and Project Time Schedule

A 3-year OMB clearance is requested to cover all data collection activities, including enrollment, follow-up and data analysis. Table A.16 below outlines the project time schedule after OMB approval. Analysis plans included conducting descriptive and modeling analyses. Results of the study will be disseminated to the scientific community through the published literature and presentation at meetings. In concert with dissemination to the scientific community, a roll-out plan will be created in collaboration with INS's and CDC's communications teams to release lay versions of the study results to the public, as warranted. Routes of communication include press releases, media interviews, INS or CDC websites, and social media.

A. 16. Project Time Schedule

	Study Year 1				Study Year 2				Study Year 3			
	Oct - Dec	Jan-Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan-Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan-Mar	Apr - Jun	Jul-Sep
Pregnancy enrollment												
Pregnancy study visits												
Male enrollment												
Male study visits												
6 month infant follow up												
Data analysis, publications												

A.17. Reason(s) Display of OMB Expiration Date is Inappropriate.

No exceptions from display of expiration date are requested.

A. 18. Exceptions to Certification for Paperwork Reduction Act Submissions

No exemptions to certification are sought.