Supporting Statement B

Zika Outcomes and Development of Infants and Children (ZODIAC) Investigation

Request for OMB approval of an Emergency ICR

OMB number xxxx-xxxx

New

Georgina Peacock
National Center for Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention
4770 Buford Highway
Atlanta, Georgia 30341
Phone: 404-498-4347
Email: ghn3@cdc.gov

July 14, 2017

Table of Contents

1. Respondent Universe and Sampling Methods

The proposed data collection to field test new and adapted assessment tools and methods will involve select groups of children at 12-24 months of age who were previously identified with laboratory and/or clinical evidence of congenital Zika virus (ZIKV) infection, with and without microcephaly, and their primary caregivers. The investigation population will include not more than 235 children in the Brazilian states of Paraíba and Ceará with laboratory and/or clinical evidence of congenital ZIKV infection, some of whom participated in a 2016 case-control investigation (OMB Control No. 0920-1011), and their primary caregivers.

Children will be recruited from a previous case-control investigation in Paraíba because these children have been well described during their infancy and have had consistent laboratory testing. Additional participants in the same age range with laboratory and/or clinical evidence of congenital ZIKV infection will be recruited from Paraíba and the neighboring state of Ceará.

The target for enrollment for the ZODIAC investigation is not more than 235 children aged 12 – 24 months old in Brazil with evidence of congenital ZIKV infection, with and without microcephaly, and their primary caregivers (total N=470). In Paraíba, all children with laboratory evidence of confirmed congenital ZIKV infection from the initial case-control investigation will be approached, as well as subsets of children with laboratory evidence of probable congenital ZIKV infection and with no laboratory evidence but with clinical indicators. In Ceará, children reported to the National Microcephaly Registry from August 2015 – May 2016 who have newborn blood specimens available for ZIKV testing or clinical indicators of congenital ZIKV infection, with and without microcephaly, will be approached. Study staff will use clinic or case-control investigation records to identify eligible children for the ZODIAC investigation.

Although we expect to approach 235 child-caregiver pairs, given recent experience in Brazil, we also expect approximately 12% to refuse to participate, which would result in a total enrollment of 195 child-caregiver pairs, distributed as follows:

Paraíba
Expect to approach: 175 child-caregiver pairs
Expect to successfully recruit: 145 child-caregiver pairs

Ceará:
Expect to approach: 60 child-caregiver pairs
Expect to successfully recruit: 50 child-caregiver pairs

A sample size of 175-200 children with laboratory evidence of congenital Zika infection but without microcephaly will yield 95% confidence interval (CI) half-widths as follows: if the sample size is 175 and the prevalence of developmental delay is 15%, the half-width will be 5.27%; if the prevalence of developmental delay is 25%, the half-width will be 6.37%. If the sample size is 200 and the prevalence of developmental delay is 15%, the half-width will be 4.93%; if the prevalence of developmental delay is 25%, the half-width will be 5.98%. Although the available number of cases reduces the power to detect an association between the presence of microcephaly and family functioning (the secondary objective of this investigation), exploratory analyses may generate hypotheses for future investigations.

2. Procedures for the Collection of Information

Study staff will use state health secretariat or case-control investigation records to identify eligible children for the ZODIAC investigation. Staff will contact families of children to be recruited in Paraíba and Ceará by phone and/or in-person and invite the child and his/her primary caregiver to participate in the proposed data collection.

Staff will recruit participants in stages. If the family does not have a phone or cannot be contacted after three phone calls, outreach workers will make one effort to visit the home in person. If all contact attempts prove unsuccessful, the interview team will record "contact unsuccessful" in the participant recruitment and tracking log (**Attachment 3).**

During the recruitment process (either by phone or in person), a project staff member will introduce himself/herself to the primary caregiver of each eligible child and provide a brief overview of the investigation (**Attachment 4**). The primary caregiver will be asked if the family is interested in knowing more about the investigation and if they would like to participate. If they are interested, investigation staff will provide additional information. They will also ask if the primary caregiver is available to accompany the child to one to two visits to a participating health facility when the child is between 12-24 months of age. (Occasionally more than two visits will be required, depending on the preference of the family and availability of specific professionals). If the primary caregiver is not available for participation in the investigation, the child will not be eligible for enrollment. If after reading the introductory script, the family is not interested in hearing more about the investigation, they will be thanked for their time and offered information about preventing mosquito-borne diseases, and other health information (**Attachment 5**). The data collection team will record "refused" in the participant tracking log (**Attachment 3**).

Participation in the proposed data collection is voluntary, and an informed consent process will precede data collection. Investigation staff will follow standard consent procedures in Brazil and will obtain written or verbal consent from the primary caregiver for participation of the caregiver and child before any data are collected and before any evaluation procedures are conducted (see **Attachment 6** for consent and assent forms). After consent has been obtained, children's health and development will be evaluated by appropriately trained personnel, and primary caregivers will be asked to provide information about the child's health and development, as well as information about their own mental health, family stress, health care needs, and family characteristics, including socioeconomic status.

Trained interviewers will administer screening and assessment instruments to the primary caregiver, as well as an interview regarding the child's health and development, and the primary caregiver's and the family's psycho-social wellbeing and economic status (**Attachments 7A, 7B, 7C, 7D, 7E, and 7F**). These instruments will be tested by data entry clerks prior to data collection.

Children will be evaluated by clinically trained professionals including a pediatrician, neurologist, pediatric audiologist, pediatric ophthalmologist, and child developmental specialist. Local personnel will be trained when available to conduct the evaluations of children, in order to build local capacity. Direct evaluation of the children will include measures of neurologic development (**Attachment 8A**), vision (**Attachment 8B**), physical growth (**Attachment 8C**), and anomalies identified through a physical examination (**Attachment 8D**), and laboratory measures of health and infection history (A**ttachment 8E**). When clinically indicated, children will be referred for neuroimaging, audiologic evaluation, and functional vision assessments and the results will be collected from the medical record. These assessments will be performed in the public health system. If needed, the investigation will pay for private clinics, identified by state health authorities, for referrals pertinent to this protocol.

ZIKV testing will be performed on stored biologic specimens collected at birth if not yet tested. A private laboratory will be hired to perform collection of blood samples by trained phlebotomists, provided parental consent is obtained, for liver and kidney function testing. Blood specimens collected from participating children will also be tested for thyroid dysfunction, lead levels, and hematocrit, any one of which may contribute to developmental delay. If consent is obtained for medical record abstraction, information will be collected from the child's medical record, including test results for other possible causes of developmental delays, such as congenital infections, as well as imaging and other clinical findings and test results for ZIKV infection, if available. (**Attachment 9**). If any of the above information was already collected for the previous case-control investigation, the information will be abstracted from the case-control investigation records rather than medical records.

Health and developmental evaluations are expected to take a total of 2-4 hours. The evaluations are generally expected to be completed in one to two separate visits, although occasionally more than two visits may be required, depending on the preference of the family and availability of specific professionals. Medical record abstraction will be done during and after the child and caregiver assessments. Initial assessments will be focused on the primary caregiver interview, and general physical, neurologic and developmental assessments, followed by an ophthalmologic exam. The order of the evaluations may vary depending on the availability of professionals needed to conduct them. The investigation team will work to minimize the number of visits by having more than one person trained and available to conduct each evaluation, and working to schedule the different types of evaluators at each visit. A list and detailed information about the information to be collected is included in **Attachment 10**.

When the team has completed data collection, parents will be provided with referrals to available services, if appropriate. The participants will be thanked for their time and given information about preventing mosquito-borne diseases and other health information (**Attachment 5**). In addition, families with a child with microcephaly will be given information about microcephaly and related concerns (**Attachment 11**).

3. Methods to Maximize Response Rates and Deal with No Response

Study staff will make multiple attempts to contact eligible families to maximize response rates. If respondents do not have a phone or cannot be contacted after three phone calls, outreach workers will make one effort to visit the home in person. If all contact attempts prove unsuccessful, the interview team will record "contact unsuccessful" in the participant recruitment and tracking log (**Attachment 2**).

In the previous (2016) case-control study of congenitally infected infants in Paraíba (OMB No. 0920-1011, 91 of 114 infants (79.8%) with microcephaly participated. Based on this experience, we anticipate a response rate of 80%.

To facilitate achieving the desired sample size, Principal Investigators at CDC and the Brazil Ministry of Health will coordinate to assure that data collection sites are located in clinics in which children with congenital ZIKV receive health care. Local public health officials will be asked to publicize the objectives of the proposed data collection to encourage recruitment for the investigation.

There are also a number of ancillary benefits to study participation that are expected to increase participation rates. Referral for follow-up related to the investigation protocol will be paid for by the investigation. Support will be offered to participating primary caregivers at every visit, including providing information on community services that may be available that may be helpful in caring for

their children. All families who are approached by the investigation team will be given information about preventing mosquito-borne diseases and other health information (**Attachment 5**). In addition, the families will benefit by knowing whether their child has any previously unrecognized health or developmental concerns as they will be given their clinical evaluation and laboratory test results. Knowing whether someone has been infected by ZIKV is considered beneficial as infection is expected to confer life-long immunity. Therefore, the person is not expected to get sick from ZIKV in the future (i.e., ZIKV infection can be excluded in the differential diagnosis if they present to healthcare in the future with similar symptoms) and the person will not present a risk to other family members. Understanding health and development status is the first step in identifying possible treatments or other services for a child with congenital ZIKV infection.

Main challenges to the success of the project include the willingness of caregivers to allow the collection of biological specimens from and clinical evaluation of the child, and to share sensitive information about themselves and their families. Proposed solutions are to ensure that trained interviewers and medical staff are of appropriate cultural backgrounds, and familiar and comfortable with discussing psychosocial and economic factors that may be of a sensitive nature, and that the interview setting affords privacy. We anticipate being able to assess non-response bias by examining participation rates by site and also by clinic. In addition, some information on non-responders may be available from clinics to assess factors associated with non-response.

4. Test of Procedures or Methods to be Undertaken

Data collection instruments were reviewed by medical personnel, laboratorians, epidemiologists and subject matter experts to ensure that they elicit essential information and that response options are appropriate and adequate. The Ages and Stages Questionnaire-3 (**Attachment 7B**), Ages and Stages Social-Emotional (**Attachment 7C**), Patient Health Questionnaire-9 (**Attachment 7D**), and the Parenting Stress Index – Short Form (**Attachment 7E**) are used in clinical practice and have previously been tested in both English and Portuguese. The Seizure Screen (**Attachment 7A**) and the Hammersmith Infant Neurologic Exam (**Attachment 8A**) are used in clinical practice and have previously been tested in English but will be tested in Portuguese for the first time through this data collection. The evaluation of cerebral palsy (**Attachment 8A**), vision exam (**Attachment 8B**), growth exam (**Attachment 8C**), physical health exam (**Attachment 8D**), caregiver questionnaire (**Attachment 7F**), and the medical abstraction form (**Attachment 9**) were developed based on previously tested instruments and will also be field tested for the first time through this data collection. CDC will translate all of the assessment tools that have not previously been translated into Portuguese and review back-translated versions before field testing. CDC will work with the developer of the Hammersmith Infant Neurological Exam (HINE, **Attachment 8A**) to test and validate a Portuguese language version of this tool, and will work with the developer of the Ages and Stages Questionnaire (**Attachments 7B, 7C**), typically used as a screening tool, to test use of its components to generate a developmental quotient (a new application of this instrument).

The instruments and procedures for the proposed data collection have been reviewed by medical personnel, neuroscientists and behavioral scientists, laboratorians, epidemiologists and other subject matter experts in the United States and Brazil. During and after this pilot, CDC staff will consider organizational, technical, and operational challenges associated with implementing the entire set of assessment tools as well as challenges with the individual assessment tools and the acceptability of each among the target population. Finally, CDC will evaluate the data collected using the assessment tools to evaluate their individual and collective potential for possible future use to improve understanding of the

longer-term health and developmental consequences of congenital ZIKV infection, the impact on affected families, and their care needs.

5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

ZODIAC Investigation designed by:

National Center for Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention
1600 Clifton Rd. NE
Atlanta, GA 30303
Principle Investigator: Georgina Peacock, Division of Human Development and Disability
E-mail: ghn3@cdc.gov
Tel. (404) 498-4347

Brazil Ministry of Health
Principle Investigator: Isabela Ornelas Pereira, Social Policy Technical Analyst
SRTVN Quadra 701, Via W 5 Norte, Lote D Edifício PO700 – 6° andar
CEP: 70.719-040 Brasil
Tel. 61-3213-8034/8004
E-mail: isabela.opereira@saude.gov.br

Data collected by:

FioTec/FioCruz
Principle Investigator, Cooperative Agreement with CDC: Marly Cruz
Avenida L3 Norte,
Campus Universitário Darcy Ribeiro
UNB Gleba A, SC4,
Edifício Fiocruz - Sala 03
70.910-900 Brasil
Tel. 55 61 3329-4790
Email: marlycruz12@gmail.com

Data analyzed by:

National Center for Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention
1600 Clifton Rd. NE
Atlanta, GA 30303
Principle Investigator: Georgina Peacock, Director, Division of Human Development and Disability
E-mail: ghn3@cdc.gov