Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS)
OMB # 0920-0010

Supporting Statement A
Revision

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- **Goal of the study:** The purpose of BD-STEPS is to evaluate factors associated with the occurrence of birth defects and stillbirths and ultimately to work to prevent major birth defects and stillbirths associated with maternal risk factors.

- **Intended use of the resulting data:** Data from BD-STEPS and the National Birth Defects Prevention Study (NBDPS) will play an important part in the decision-making process that determines federal research agendas, birth defect prevention activities, and the direction of funding programs such as cooperative agreements.

- **Methods to be used to collect:** Data will be collected via telephone interviews and online questionnaires. Additionally, participants will be asked to consent to release of reportable infectious disease information and the collection of leftover newborn screening bloodspots.

- **The subpopulation to be studied:** BD-STEPS will interview mothers of infants with birth defects who are identified through the birth defects surveillance system in each participating state; control infants (whose mothers will be invited for interview) are randomly selected from electronic birth certificates or birth hospitals for the same population as cases.

- **How data will be analyzed:**
  Univariate and bivariate statistics (e.g., percentages, Chi-squared tests) will be used to describe the distribution of potential risk factors among cases and controls. Logistic regression will be the primary analytic tool used for studying associations between categories of birth defects and potential risk factors; relative risk estimates will first be calculated without consideration of potentially confounding variables, then important covariates such as maternal age and education will be included. Other advanced statistical methods (e.g., machine learning, Bayesian analysis) will be used as appropriate. We will also look for evidence of gene-environment interaction in analysis of NBDPS genetic data.

Birth Defects Study To Evaluate Pregnancy exposureS

A. Justification

A.1. Circumstances Making the Collection of Information Necessary

This Information Collection Request is submitted under the classification "Revision". The length of this data collection requested for Office of Management and Budget (OMB) approval is three years. The National Center on Birth Defects and Developmental Disabilities (NCBDDD) at the Centers for Disease Control and Prevention (CDC) is making this request as authorized by Section 317C of the Public Health Service Act (42 U.S.C. 247b-4; **Attachment A**). This revision is for additional questions to the maternal questionnaire on infections, travel, and marijuana use during pregnancy; the addition of five new birth defect case groups; a linkage to reportable infectious disease data; and a change in the incentive/compensation structure. This revision also includes the removal of the medical record review that was not implemented and for which there are no current plans for implementation.

The previously approved revision for this study (OMB # 0920-0010, expiration 02/29/2020) changed the title from the National Birth Defects Prevention Study (NBDPS) to the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS). Both NBDPS and the BD-STEPS are conducted by the congressionally mandated Centers for Birth Defects Research and Prevention (CBDRP). Seven CBDRP currently participate in BD-STEPS: Arkansas (AR), California (CA), Iowa (IA), Massachusetts (MA), North Carolina (NC), New York (NY), and CDC/NCBDDD's Division of Congenital and Developmental Disabilities (DCDD) which serves as the site of record for Georgia (GA).

With another round of BD-STEPS funding (2018-2023), the CBDRP collaborative will expand on the knowledge learned from NBDPS and the activities of BD-STEPS to date. The intent of the next round of funding is to carry out the same BD-STEPS study design with minor changes, which have been determined to be necessary, and which are detailed in Section A15. Explanation for Program Changes or Adjustments.

Background

Birth defects are associated with substantial morbidity and mortality in the United States. About one in every 33 babies is born with a birth defect. Birth defects contributed to more than 1 million hospital stays in the U.S. in 2013, resulting in $22.9 billion in hospital costs. Birth defects are the leading cause of infant mortality and the fifth leading cause of loss of potential years of life before age 65. One in five infant deaths is due to birth defects. Preventing major birth defects associated with maternal risk factors is one of the key priorities for NCBDDD.

However, to date, primary preventive measures are available for only a few birth defects. For example, vaccination programs have reduced the incidence of congenital rubella syndrome, Rh hemolytic disease of the newborn can be prevented by appropriate medical practice, and genetic counseling can provide parents with information about the increased risk of Down syndrome associated with advanced maternal age. Perhaps most importantly, folic acid intake before and during pregnancy can prevent many cases of fatal or permanently disabling neural tube defects such as anencephaly and spina bifida.

For most birth defects, however, the causes are not known, making prevention efforts challenging to develop. This continuing burden justifies reasonable attempts to reduce the prevalence of birth defects. To help reduce birth defects among U.S. babies, in 1996 Congress directed the CDC to establish Centers of Excellence for Birth Defects Research and Prevention. The mandate was formalized with passage of the Birth Defects Prevention Act of 1998 (see **Attachment A** for Public Law 105-168). This Act amended Section 317C of the Public Health Service Act (42 U.S.C. 247b-4) and authorized CDC to (1) collect, analyze, and make available data on birth defects; (2) operate regional centers that will conduct applied epidemiological research for the prevention of birth defects; and (3) provide the public with information on preventing birth defects.

In response to this mandate, the Division of Congenital and Developmental Disorders (DCDD) obtained OMB clearance for data collection that is carried out by the Centers for Birth Defects Research and Prevention (CBDRP). The CBDRP's first research effort was the National Birth Defects Prevention Study (NBDPS), which began data collection in 1997 and ended in 2013. The

CBDRPs transitioned from NBDPS to the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS), which began data collection in 2014. See **Attachment E** for a current list of BD-STEPS Centers. One of the main activities for each Center is to conduct BD-STEPS in their state (see section A.4).We are currently seeking a revision to OMB clearance to continue and expand BD-STEPS data collection.

In BD-STEPS, pregnancies affected by birth defects are identified through existing population-based birth defects surveillance systems in each participating state that has legislative authority to collect information on infants with major congenital malformations. Control-infants are live-born infants without a major birth defect selected randomly from vital records (birth certificates) or from hospital birth logs, and represent the birth population from which the case infants were identified. Mothers of case and control infants are interviewed by phone about their medical history, pregnancies, environmental exposures, and medications. Mothers of infants who are stillborn without major birth defects are also interviewed by phone for two Centers. In states that allow retrieval of blood spots, BD-STEPS participants are asked for permission to share a portion of the newborn blood spot for the child who is part of the study, and for mothers of multiples, the co-siblings of this child.

Currently, OMB approval (OMB 0920-0010; expiration February 29, 2020) encompasses the data collected from six states and DCDD, CDC in Atlanta to conduct 300 interviews (200 cases and 100 controls).

For this revision, we are proposing the following changes: add questions to the maternal interview about infections, travel, and marijuana; add five additional birth defects that are eligible for inclusion into the study; request maternal consent to link to data on notifiable infectious diseases from state health departments; and add a post-interview incentive to acknowledge the time taken by the mother to complete the interview.

A.2. Purpose and Use of the Information Collection

Data from this information collection play an important part in the decision-making process that determines federal research agendas, birth defect prevention activities, stillbirth prevention activities, and the direction of funding programs such as cooperative agreements. The purpose of BD-STEPS is to identify modifiable maternal exposures in early pregnancy that may increase the risk for having a pregnancy affected by birth defects and to test hypotheses for gene-environment interactions involved in the etiology of birth defects. Information collected in the interview (**Attachments F1/F2**) provides data for the evaluation of suspected new teratogens, mutagens, or environmental agents that are not prevalent enough to cause epidemics. For example, the information on family history of birth defects is useful in assessing the degree to which subsequent children in a family are at risk of having a birth defect or adverse outcome. The data gathered on maternal occupation is useful in assessing the impact of the work place on reproductive outcome. The interviews also offer the possibility of identifying protective factors. The supplemental telephone interview allows for the identification of modifiable causes of stillbirth in infants with and without birth defects. The DNA extracted from the bloodspot samples will be used to study genetic susceptibility to the effects of environmental agents. For women with multiple births (e.g. twins, triplets), limited data and bloodspots from all infants who were part of the multiple birth will provide unique genetic data for analyses. Using novel genetic approaches, it is possible to evaluate the role of genetic differences at specific gene loci and their interaction with other genes or specific environmental exposures in the etiology of birth defects.

Data from this information collection will continue to provide the nation with a source of information on potential causes of birth defects and will serve as a mechanism for identifying new substances in the environment that are harmful to fetal development. Over 300 manuscripts have already been published using NBDPS data (see Section A.16), and many more manuscripts are proposed and currently being written. The findings are interpreted with caution and all publications acknowledge the strengths and limitations of the study design. The information provided is critical to the mission of the Public Health Service to reduce morbidity and mortality due to congenital malformations.

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

BD-STEPS participants are recruited to complete an interview questionnaire that is administered using a computer assisted telephone interview (CATI) (**Attachments F1/F2**). The average time to complete the interview is approximately 55 minutes. The BD-STEPS CATI is designed to ascertain only information that is pertinent and useful in identifying possible risk factors associated with adverse reproductive outcomes. The CATI has extensive question skip logic that eliminates duplicative responses in order to reduce burden on participants. The CATI makes it possible to complete the interview in segments so that participants have the option of completing the interview in several sessions rather than all at once. Standard data elements, such as demographic information, that are available from an existing source, either a birth/death certificate or hospital records, are not collected during the telephone interview to reduce the burden on participants.

To advance the use of information technology and reduce burden on participants, an online questionnaire was developed in order to query in-depth questions about maternal occupations. Participants are flagged in the CATI (**Attachments F1/F2**) then recruited to complete an online questionnaire if they report working in any of the occupational categories of interest (healthcare workers, farm workers, janitors/cleaners, hairdressers/cosmetologists, teachers, food service workers, office workers, and electronic equipment operators). Most CBDRPs send a standardized introductory email (one CBDRP sends the invitation as a paper copy letter) to each participant; the introductory communication includes information about the online questionnaire and a link to the questionnaire. The online questionnaire includes occupation-specific questions and an informed consent page (the eight occupation-specific questionnaires including the introductory communication and the informed consent page is included as **Attachment G1-G8**). If the online questionnaire is unavailable, participants are provided with a paper questionnaire (**Attachment G1A-G8A**) only when participants choose not to complete the questionnaire online.

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

Efforts to identify duplication include periodic systematic reviews of the scientific literature and frequent discussions with birth defects researchers at federal agencies and research institutions across the United States as facilitated by Center and CDC contacts. BD-STEPS is the only population-based case-control study of risk factors for the 22 selected birth defects (see **Attachment H** for a list of birth defects and case definitions studied in the BD-STEPS) being conducted in the U.S. at this time, including the five birth defect categories we are requesting to include in the study (microcephaly, holoprosencephaly, anterior segment eye defects, posterior segment eye defects, and arthrogryposis). BD-STEPS is also conducting research on risk factors for stillbirths without major birth defects (see **Attachment I1/I2** for the definition and explanation of stillbirths without birth defects). The questionnaire is included as **Attachment J1/J2**.

All of the BD-STEPS Centers are using the same processes for identifying eligible cases and controls, participant contact, and data processing. BD-STEPS interviews for all the sites are done by one central CDC-funded contract interviewing facility, which provides consistency and efficiency over interviews being conducted separately at each site. Collaboration among the Centers and CDC is essential for the success of BD-STEPS because it allows scientists with differing expertise to work together, substantially improving the ability to better understand birth defect risk factors. Because birth defects are rare, it takes many years to accumulate enough cases of a particular defect to have the power to study risk factors for that defect. It may also enable researchers to identify rare exposures, such as genetic variations, that are associated with the more common birth defects.

The BD-STEPS case-control study provides a unique and unprecedented opportunity to evaluate risk factors for individual birth defects from livebirths and stillbirths. A number of case-control studies of birth defects have been conducted previously, but because individual birth defects are relatively rare, it has been difficult to conduct a study large enough to provide the necessary power to evaluate risk factors for specific and potentially rare defects. Several surveillance systems collect maternal and infant data that provide state- and national-level prevalence

estimates of maternal behaviors and experiences before, during, and after pregnancy. These surveillance systems can be used to assess a limited number of birth defects risk factors for which information is included in the surveillance system, as well as to identify unusual patterns of birth defect occurrences, but do not have sufficient samples of rare birth defects or detailed exposure assessments that the BD-STEPS case-control study contributes.

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

No small businesses are or will be involved in this study.

A.6. Consequences of Collecting the Information Less Frequently

Because individual birth defects are relatively rare, it is important to collect data on many research subjects to provide the necessary statistical power to evaluate risk factors for specific defects. In addition, many risk factors are relatively rare, and more data will provide more statistical power to examine these rarer exposures among pregnant women. If less data were collected, fewer risk factors and fewer birth defects would have sufficient statistical power to be analyzed. This same principle applies to both the genetic and interview data collected for BD-STEPS.

There are no legal obstacles to reduce the burden.

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

The project fully complies with all of the guidelines of 5 CFR 1320.5.

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

A. A copy of the agency's 60-day Federal Register Notice is attached (60-day Federal Register Notice **Attachment B**). The notice, as required by 5 CFR 1320.8 (d), was published on March 4, 2019 *(Volume 84, Number 42, pages 7374-7375).* No comments were made.

B. The principal investigators at each CBDRP currently work collaboratively with CDC scientists on scientific analysis and study conduct. BD-STEPS has a Data Sharing Committee with representatives from each Center with the ongoing task of deciding how data will be equitably shared for analysis purposes. This committee is responsible for review of all protocols for data analysis as well as addressing human subjects' issues, data access, collaboration, and authorship. In addition, while data collection for NBDPS has ceased, data analysis is ongoing and will continue to have Data Sharing review by collaborating scientists.

The **Coordinating Council** for BD-STEPS consists of the Principal Investigators for each of the study Centers and has the ongoing responsibility of conducting study business and making decisions about study conduct. The scientists involved in BD-STEPS and NBDPS represent the greatest concentration of expertise and experience on birth defects in the United States (please see **Attachment K** for a detailed list of collaborators). There have been no major problems identified through these consultations.

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

Research suggests that the use of tokens of appreciation results in increased response rates and indicates to respondents that the investigators believe their participation is valuable. Tokens of appreciation may also help prevent biases introduced by lower participation rates among the economically disadvantaged. Literature examining the benefit of tokens of appreciation for participation was summarized by Yu (Yu J, et al. "A quantitative review of research design effects on response rates to questionnaires." *J Marketing Res* 1983; 20:36-44). It reviewed 497 response rates found in 93 journal articles and found that response rates increased with monetary and non-monetary incentives.

The NBDPS began providing tokens of appreciation to participants for the maternal interview in January 2000, at which time a $20 money order was included in the introductory interview packet. When the $20 money order was added, participation rates for both cases and controls initially increased then stabilized between approximately 60 and 70%. Due to decreased response rates for BD-STEPS compared to NBDPS, the Coordinating Council voted to send a $30 gift card to women upon completing the telephone interview, in addition to the $20 gift card included in the introductory packet.

Data continue to support the use of monetary incentives, including prepaid incentives

- Prepaid incentives yield higher response rates than promised incentives or no incentives
- Monetary incentives yield higher response rates than gifts
- Response rates increase with increasing amounts of money, though not always linearly
- Effect of incentives has not changes over time, although baseline response rates have dropped substantially
- References:
    - Singer E, Ye C. "The use and effects of incentives in surveys" *The ANNALS of the American Academy of Political and Social Sciences*; 2013; 112-141.
    - Cantor D, O'Hare BC, and O'Connor KS. "The use of monetary incentives to reduce nonresponse in random digit dial telephone surveys" *Advances in Telephone Survey Methodology* 2008; 471-498.
    - Edwards P, et al. "Increasing response rates to postal questionnaires: systematic review" *BMJ* 2002; 324(7347):1183.
    - Church AH. "Estimating the effect of incentives on mail survey response rates: A meta-analysis" *Public Opinion Quarterly* 1993; 57(1):62-79.
    - Singer meta-analysis 1999 interviewer-mediated surveys

Focus groups were conducted to assess factors related to participation in the biologics components of NBDPS (buccal cell collection) among mothers who participated in the NBDPS interview. Participants reported that monetary incentives increased perceived study legitimacy.

- Jenkins MM, et al. “Qualitative assessment of study materials and communication strategies used in studies that include DNA collection” *American Journal of Medical Genetics (Part A)*;2011;155:2721-2731,

The online occupational questionnaire is offered to participants who reported certain occupations during the interview (see **Attachment G1-G8**) to ask more in-depth questions about potential exposures in the workplace. If the BD-STEPS online occupational questionnaire is completed, a $10 gift card is mailed to the respondent.

The token of appreciation amount for the bloodspot consent request is ten dollars. The BD-STEPS Coordinating Council voted to implement $10 tokens of appreciation for the bloodspot consent.

For the new infectious disease linkage consent request, a $10 gift card will be sent to mothers, with a thank you letter, as a token of appreciation after a signed consent form is returned (see **Attachment L and M,** respectively) or verbal consent is obtained (see **Attachment N)**. The $10 value was chosen because it is consistent with the amount provided for completing the online questionnaire and returning the newborn screening bloodspot consent.

For the two Centers participating in the stillbirth component of BD-STEPS (AR and MA), a $10 gift card is sent to mothers as part of the introductory packet for this part of the study **(Attachment O1/O2)**. After the supplemental telephone interview is completed, a $10 gift card will be mailed to the respondent along with the stillbirth thank you letter (**Attachment P1/P2**); the additional gift card after a participant completes the supplemental telephone interview is submitted as part of this revision.

A.10. Protection of the Privacy and Confidentiality of Information Provided by Respondents

The NCBDDD Privacy Act Officer reviewed this OMB application and has determined that the Privacy Act is applicable. A contractor is used to conduct all interviews for the BD-STEPS

Centers. Full names of respondents must be collected to enable the study goals to be achieved. Records will be covered under the CDC Privacy Act system of records 09-20-0136, Epidemiologic Studies and Surveillance of Disease Problems. BD-STEPS is based on the previous experience of the NBDPS and BDRFS, which was initiated at CDC and had 308(d) confidentiality assurance protection. The BDRFS was expanded in 1997 through cooperative agreements. The activities of BD-STEPS, like the NBDPS, are both intramural and extramural, consisting of one CDC operated site in Atlanta, Georgia, and six CDC-funded cooperative agreements in six other states. Because all sites (except the CDC's Atlanta site) were funded by cooperative agreements and protection was needed for data at each site, it was determined by the CDC Office of General Counsel and the CDC Confidentiality Officer that a 301(d) Certificate of Confidentiality was the appropriate confidentiality protection. NBDPS received a Certificate of Confidentiality for the eight original study sites in August 1999, and the latest renewal was signed for BD-STEPS on February 2014. BD-STEPS continues to maintain a Certificate of Confidentiality but a hard-copy of a Certificate is no longer issued by CDC due to changes in Section 301(d) of the Public Health Service Act (PHS) Act, which authorizes the use of Certificates, that was amended by the 21st Century Cures Act. The amended Act states that the Secretary of HHS shall issue Certificates to persons engaged in biomedical, behavioral, clinical, or other research activities in which identifiable, sensitive information is collected. Due to this change, CDC-supported research started or ongoing after December 13, 2016, and in which identifiable, sensitive information is collected, is protected by a Certificate. Researchers conducting research with a Certificate are required to protect the privacy of research subjects in accordance with Section 301(d) of the PHS Act. Language referring to Certificates was included in the terms and conditions for this funding - Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS) II RFA-DD-18-001.

The Certificate of Confidentiality protects participants by preventing study staff from being forced under a court order or other legal action to identify study participants or provide individually identified data. The Certificate also supplies additional assurance to both participants and CDC’s cooperating researchers that the data collected will be kept confidential and will not be subject to potential release from a wide variety of sources. Because the topics of the study are sensitive, respondents are more likely to participate if they are assured their identity

is secure and will not be subject to review by people outside of the research process. See telephone interview consent script, bloodspot retrieval written and verbal informed consents for mothers of singletons and multiples, online questionnaire consent and the infectious disease linkage consent, as well as the supplemental telephone interview consent script, in **Attachments Q1/Q2, R1/R2, S1/S2, T1/T2, U1/U2, G1-G8, L1/L2-M1/M2, and V1/V2** respectively.

The data to be covered by 301(d) confidentiality certificate protection include the interviews (phone and online), clinical data, infectious disease information collected, and results of testing on biological samples collected for BD-STEPS. Each site operates a state surveillance program established by law that was operational prior to the Center's study. Surveillance data already in the possession of the sites is not to be included under the certificate. The data are properly safeguarded. Access to individually identified study information is limited to a very small number of authorized study personnel. All personnel with access to study data must sign the CBDRP Confidentiality and Data Use Oath (**Attachment W**).

Privacy Impact Assessment

I. Description of how the information will be shared and for what purpose:

As described in Section A8, NBDPS and BD-STEPS data will be shared for analysis purposes. The Data Sharing committee, made up of collaborating, study-affiliated scientists, is responsible for review of protocols for data analysis as well as addressing human subjects' issues, data access, collaboration, and authorship. In addition, we expect data from participant specimens will be analyzed as part of NIH-funded future studies, and the NIH Genomic Data Sharing (GDS) policy requires data from NIH-supported genomic studies be deposited into NIH data repositories, including the database of Genotypes and Phenotypes (dbGaP).

II. Overview of the Data Collection System

BD-STEPS data, are collected, as NBDPS data were, in part by questionnaire using a computer assisted telephone interview (CATI). The average time to complete the BD-STEPS CATI interview is estimated to be 55 minutes where the NBDPS CATI lasted one hour. The interview used in BD-STEPS is designed to ascertain only questions that are pertinent and useful in identifying possible risk factors associated with adverse reproductive outcomes. The CATI

makes it possible to complete the interview in segments so that participants have the option of completing the interview in several sessions rather than all at once. The BD-STEPS CATI is included as **Attachment F1/F2**. After the BD-STEPS CATI is completed, participants with certain occupations are invited to complete a 20-minute online questionnaire (See **Attachment G1-G8**).

III. Description of Information to be Collected

Contact information (phone numbers and mailing addresses) for the subjects is collected through existing surveillance programs at individual CBDRP, encrypted, and sent from the individual CBDRP to the interviewing facility via the CDC-provided Secure Access Management Services (SAMS) system. Maternal interviews are completed at the interviewing facility using a computer assisted telephone interview (CATI) system, and information in identifiable form (IIF) is collected, maintained and passed through the CDC-developed database to facilitate the compilation of data for the CBDRP. The following are all categories of IIF collected: name, date of birth of mother, father, and baby, mailing address, phone numbers, email addresses, medical information and notes, and leftover newborn bloodspots (for singletons and multiple births). Other categories of non-IIF data include pregnancy history (i.e. number of previous pregnancies and fertility treatments), maternal conditions and illnesses (i.e. diabetes, high blood pressure and infections), family history, lifestyle and behavioral factors (i.e. stress, alcohol use, and marijuana use), medication use, environmental exposures, travel. The online questionnaire, sent to a subset of participants, collects detailed information about certain occupations (see **Attachment G1-G8**). In addition, the planned linkage to reportable infectious diseases data will include a consent request for release of these data by the state health department.

A Privacy Impact Assessment was signed by Beverly Walker on July 26, 2017. We provide a PIA overview below (see **Attachment X** for signed *Privacy Impact Assessment Form*).

IV. Whether individuals are informed that providing the information is voluntary or mandatory

According to the guidance provided, participants receive the Privacy Act Statement as it pertains to this information collection (see **Attachment DD**). The participants are informed in several

places before the interview takes place that participation is voluntary: the question and answer sheet and the human subjects fact sheet that are mailed to the mother before the interview, and the informed consent telephone script that is read to the mother before the interview. See Section A11 for more information on the emphasis of the voluntary nature of participation.

V. Opportunities to consent, if any, to sharing and submission of information

Consent is obtained before collection of data. Oral consent is obtained before the CATI questionnaire is administered. For subjects eligible for the online questionnaire, the first page of the online questionnaire contains the consent and participants must indicate consent to proceed with the survey. For Centers requesting bloodspots there is written and verbal consent. There is also a written and verbal consent for the release of reportable infectious diseases information from the state health department. For subjects eligible for the supplemental telephone interview, verbal consent is obtained before the CATI questionnaire is administered. See attached interview telephone consent script, the online questionnaire consent, bloodspot retrieval written and verbal informed consents for mothers of singletons and multiples, the release of reportable infectious diseases information written and verbal consent, and the supplemental telephone interview consent in **Attachments Q1/Q2, R1/R2, S1/S2, T1/T2, U1/U2, G1-G8, L1/L2-M1/M2, and V1/V2** respectively.

VI. How the information will be secured

As mentioned above (Privacy Impact Assessment, Section II), contact information for the subjects will be encrypted and sent from the individual CBDRP to the interviewing facility via the CDC provided Secure Access Management Services (SAMS) system. Any PII collected during the process is stored within a column-level encrypted Microsoft SQL Server database. Biologic samples obtained as part of NBDPS and BD-STEPS are stored in a secure manner without identifiers (with the exception of study identification number) in secure storage facilities.

VII. Whether a system of records is being created under the Privacy Act

As mentioned above (Section A10), records are covered under the CDC Privacy Act system of records 09-20-0136, Epidemiologic Studies and Surveillance of Disease Problems.

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

IRB Approval

CDC IRB approval for the NBDPS and now BD-STEPS is renewed yearly; current approval expires January 29, 2020 (See **Attachment D** for current CDC IRB approval letter). CDC IRB approved the changes submitted in this revision (See **Attachment C1 and C2**).

The maternal BD-STEPS interview asks questions about topics that may be considered sensitive, including alcohol use, pregnancy history, history of sexually transmitted diseases, history of depression and anxiety, and use of fertility medications and procedures. These topics are included in the study because several reports have linked these factors to birth defects, and these associations need further clarification. The interviewers are trained to emphasize not only the voluntary nature of the entire interview but the respondent's prerogative to not answer specific questions. As mentioned, there are three places before the interview takes place where the mother is informed that her participation is voluntary: the question and answer sheet and the human subjects fact sheet that are mailed to the mother before the interview, and the informed consent telephone script that is read to the mother before the interview.

The informed consent telephone script (**Attachment Q1/Q2**) also informs the mother that there are some questions about sensitive issues in the interview and that she can choose not to answer any specific questions. The script also emphasizes that the mother's answers will be kept confidential.

The study obtains written informed consent for retrieval of previously collected newborn bloodspots for singletons and multiples (**Attachment R1/R2 and T1/T2**) in some states while some states obtain verbal informed consent for newborn bloodspots for singletons and multiples (**Attachment S1/S2 and U1/U2**. Again, the participants are reminded in the consent (**Attachments R1, S1, T1 and U1**) that all parts of the study are voluntary and all data gathered in the study are stored without names attached. The protection afforded by the Certificate of Confidentiality is also explained again in the written and verbal consent for the release of reportable infectious diseases results (**Attachment L and N**).

The study will also request written and verbal informed consent for release of previously collected reportable infectious disease information from each state's National Notifiable Diseases Surveillance System (**Attachment L and N**). Again, the participants are reminded in the written consent that all parts of the study are voluntary and all data gathered in the study are stored without names attached. Along with the in infectious disease consent form, participants will receive an infectious disease frequently asked questions that provides additional information on access and results of requested information among other questions (**Attachment Y1/Y2).**

The online questionnaire includes a one-page informed consent. This consent, like the telephone and written consents described, explains that the mother is "free to stop the survey at any time," and provides assurance that answers will be kept confidential (**Attachment G1-G8**).

Finally, the telephone informed consent script for the supplemental telephone interview (**Attachment V1/V2**), like the previously described consents, explains that the mother can choose not to answer any specific question and that answers will be kept confidential.

The BD-STEPS interview data are compiled on a secured server at CDC.

A.12. Estimates of Annualized Burden Hours and Costs

The interview is estimated to take approximately 55 minutes and is 10 minutes longer than the previously OMB-approved interview. The BD-STEPS interview is titled "Birth Defects Prevention Study: Computer Assisted Telephone Interview" (see **Attachment F1/F2**). For the five Centers not participating in the stillbirth component of the study, a maximum of 370 interviews are planned per year per center, 270 cases and 100 controls; for the two Centers participating in additional stillbirth interviews, 590 interviews are planned per Center, 270 cases with birth defects, 100 controls, and 220 stillbirths without birth defects. With seven Centers and a maximum of 3,030 interviews, the maximum interview burden for all centers combined would be 2,778 hours per year over three years. The 55 minute burden includes the time for the telephone consent script (**Attachment Q1/Q2**) which is reviewed with the mother at the beginning of the call to collect the information via the CATI interview.

Five of the seven BD-STEPS Centers request consent for retrieval of leftover newborn bloodspots. If a maximum of 2,590 interviews would be expected for seven Centers, a maximum of 1,850 would be expected for five Centers requesting consent for retrieval of leftover newborn bloodspots (excluding stillbirths, for which newborn bloodspots are not available). A maximum of 15 minutes would be expected for the participant to read the bloodspot retrieval consent request and sign the consent form (**Attachment R1/R2 and S1/S2**). The anticipated maximum burden for bloodspot consent would be 463 hours annually.

With a maximum of 2,590 interviews planned annually, and approximately one third of the respondents eligible for the online questionnaire (selected based on reporting occupations queried in the questionnaire), a maximum of 830 women would receive the online questionnaire. Completion of the online questionnaire is estimated to take 20 minutes including reading introductory communication. The anticipated maximum burden for the online questionnaire is 277 hours annually.

We will request the release of reportable infectious diseases information from all women who complete the CATI. Of the 2,590 interviews planned annually, a maximum of 2,590 women would receive the infectious disease information request. Based on experience with consent forms, we expect the review, signing and mailing of the release of reportable infectious diseases information (**Attachment L1/L2**) to take a maximum of 15 minutes for participants. The anticipated maximum burden for the reportable infectious diseases information is 650 hours annually.

In the two Centers participating in the supplemental interview, mothers of infants with or without birth defects that are stillborn and controls are asked to participate in a supplemental telephone interview. The 25 minute supplemental interview includes the time for informed consent. Based on a maximum of 640 women to be interviewed with the supplemental questionnaire, the maximum burden time would be 267 hours annually.

The total estimates of annual burden hours for all activities for all individuals for all Centers is 4,433 hours. The estimates of annualized burden hours represent the total population however due to lower participation rates (no more than 60%), the actual burden will be lower as well.

Table A.12-1 Estimates of Annualized Burden Hours*

Respondents	Form Name	Number of Respondents*	Number of responses per respondent	Avg. burden per response (In hours)	Total Burden Hours
Mothers (interview)	Telephone Consent Script (Attachment Q)/BD-STEPS Computer Assisted Telephone Interview (Attachment F)	3,030	1	55/60	2,778
Mothers (consent for bloodspot retrieval)	Consent for bloodspot retrieval (Attachment R, S, T, and U)	1,850	1	15/60	463
Mothers (online occupational questionnaire)	Online Occupational Questionnaire (Attachment G1-8)	830	1	20/60	277
Mothers (infectious disease release review)	Infectious Disease Request Form (Attachment L and N)	2,590	1	15/60	648
Mothers of all AR/MA stillbirths and controls (supplemental telephone interview)	Telephone consent and supplemental interview (Attachment J)	640	1	25/60	267
TOTAL					4,433

* These numbers are for the extreme situation that we would have 100% complete participation. We expect ~60% participation for the Mothers (interview) at best.

Table A.12-2 Estimated Annualized Burden Costs

Type of Respondents	No. of Respondents	No. Reponses per Respondent	Avg. Burden per Response (in hours)	Total Burden Hours	*Hourly Wage Rate	Total Respondent Costs
Mothers (interview)	3,030	1	55/60	2,778	$10.00	$27,780
Mothers, (consent for bloodspot	1,850	1	15/60	463	$10.00	$4,630

retrieval)						
Mothers (online occupational questionnaire)	830	1	20/60	277	$10.00	$2,770
Mothers (infectious disease record review)	2,590	1	15/60	648	$10.00	$6,480
Mothers of all AR/MA stillbirths and controls (supplemental telephone interview)	640	1	25/60	267	$10.00	$2,670
TOTAL						$44,330

***Approximately 75% of women of childbearing age do participate in the U.S. workforce (see http://www.bls.gov/opub/ted/2000/feb/wk3/art03.htm). A subset of these childbearing women are part-time and not full-time workers. We have used the National Compensation Survey to aid in our calculation of the hourly wage rate for our table entitled "Estimated Annualized Burden Costs" (please see the U.S. Department of Labor publication entitled: "National Compensation Survey: Occupational Wages in the United States, May 2017" located at http://www.bls.gov/oes/current/oes_nat.htm). We have thus calculated an hourly wage rate of $10.00 for the respondents for this ICR.**

Interview costs: A respondent mother can have time costs for the interview. An interview is estimated to take 55 minutes, and an hour of respondent time is estimated to cost $10. A maximum of 3,030 are planned, resulting in a maximum interview burden of 2,778 hours for all Centers per year ($27,780 per year).

Bloodspot consent costs for five Centers: The anticipated maximum burden for bloodspot consent retrieval hours per year for the respondent mothers is 463 hours for all Centers per year ($4,630 per year).

Online questionnaire costs: The anticipated maximum burden for online questionnaire completion per year for respondent mothers is 277 hours for all Centers per year ($2,770 per year).

Infectious disease records review costs: The anticipated maximum burden for notifiable infectious disease record review per year for respondent mothers is 648 hours ($6,480 per year).

Supplemental telephone interview cost for mothers of stillbirths and controls for two Centers: The anticipated maximum burden per year for respondent mothers is 267 hours ($2,670 per year).

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

There are neither (a) total capital and start-up costs, nor (b) operation, maintenance, and purchase of services costs for respondents or record keepers resulting from the collection of information.

A.14. Annualized Costs to the Federal Government

See Table A.14-1 for a total annual cost estimate for one year to conduct the entire study of the BD-STEPS. BD-STEPS II RFA-DD-18-001 activities began in September 2018. It is anticipated that costs in future years will be comparable to those shown in the table with appropriate adjustments for budget changes, inflation, and salary increases.

Table A.14-1: Estimates of Annual Cost to the Government

	CDC and Contract Personnel*	FTEs	Costs* (dollars)
Federal Government Personnel Costs	Epidemiologist, GS-15	.2	38,640
	Health Scientist, GS-14	.9	158,400
	Epidemiologist, GS-14	.8	132,240
	Epidemiologist, GS-14	.5	77,000
	Medical Officer, GS-14	.5	108,750
	Health Scientist, GS-12	.5	57,650
	Data Manager, GS-13	1	163,600
	Data Programmer, GS-14	.5	75,500
Federal Government Other Direct Costs	Printing		4,000
	Postage		3,000
	Office Supplies		3,000
	Travel		6,000
	Computer Equipment		2,000
Contractor Direct Labor	ORISE	1	76,000
	Programmer Q&A	.25	44,645
	Project Coordinator	1	129,139

	Medical Officer	.5	144,634
	Epidemiologist	1	186,835
	Study Coordinator	.8	125,700
	Data Management	1	159,220
Interview contract	Total Interview contract costs		1,087,773
TOTAL COSTS			2,783,726

*CDC personnel cost includes salary, benefits and physicians pay (if applicable). Contractor costs include direct and indirect cost plus profit are fully burdened.

A.15. Explanation for Program Changes or Adjustments

This revision includes additional questions to the maternal questionnaire on infections, travel, and marijuana use during pregnancy; the addition of five new birth defect case groups; a linkage to reportable infectious disease data; and a change in the incentive/compensation structure. This revision also includes the removal of the medical record review that was not implemented and for which there are no current plans for implementation.

1. Additional questions for the maternal computer assisted telephone interviews (CATI) (**Attachment F**) on infections, travel, and marijuana use during pregnancy.
   The outbreak of Zika virus has shown that novel causes of birth defects can be identified at any time. During the CDC emergency response it became clear that the mosquito-borne and sexually transmitted flavivirus is associated with devastating birth defects when infection occurs during pregnancy. To allow for further investigation of infectious causes of birth defects new questions about possible exposure to infectious disease, including through travel, will be added to the questionnaire. In addition, as marijuana has become, legal to use for medicinal and/or recreational purposes in an increasing number of states, it is important to understand the potential impact of this exposure on the risk for birth defects and stillbirth. Burden hours have been revised to include this additional data collection. See **Attachment Z** for the justification of new questions: infections, travel history, and marijuana use sections.

2. Consenting participating mothers to link to state-based notifiable infectious disease reports. (**Attachments L1/L2 and N1/N2**)
   In order to better understand what infections may contribute to birth defects risk and other pregnancy problems, all mothers who complete the computer assisted telephone interview (CATI) will receive a form requesting their consent to access information on reportable infectious diseases from their state health department. The introduction of the notifiable infectious disease request is included with the CATI thank you letter (**Attachment AA1/AA2 and BB1/BB2**). The participants will be sent an incentive upon returning a signed consent form. In addition, burden hours and cost estimates have been revised to include this additional data collection.

3. Addition of five eligible birth defect case groups for defects that are likely to be related to maternal infection during pregnancy. (**Attachment H)**
   Additional defects suspected to be associated with prenatal infectious disease will be added as part of a focus on infectious causes of birth defects.

4. Changing the incentive structure to promote participation.
   Currently, and as far back as January 2000 in NBDPS, eligible subjects are sent a $20 gift card as a token of appreciation for considering participation in the study. To account for inflation and the well-documented decrease in participation across many studies that employ telephone-based interviewing, participants will now be offered an additional incentive upon completing the telephone interview: a $30 gift card included with the thank you letter mailing (**Attachment AA1/AA2 and BB1/BB2**). To date an incentive of $10 is sent to eligible participants with the consent form for use of newborn bloodspots. With our new remuneration structure, all participants who complete the interview will receive $30 after completion of the interview, therefore this token of appreciation will now be sent after the newborn bloodspot consent form is received or verbal consent is obtained. Participants will also be provided a separate $10 token of appreciation when the consent for linkage to reportable infectious disease data is received. (**Attachment L1/L2**). Mothers who complete the stillbirth supplemental CATI will continue to receive a $10 incentive with the introductory packet, and will now also receive a $10 gift card

with the thank you letter mailing after completing the Stillbirth supplement telephone interview (**Attachment P1/P2**).

These changes, in combination, increase the total expected burden hours for BD-STEPS data collection from the previous OMB approved data collection by 1,399 hours. With the inclusion of new birth defects (an increase of 665 respondents) and new questions added to the CATI (infection, travel, and marijuana use), the estimated additional burden for the CATI (maternal telephone interview) in an increase of 1,004 hours. The number of respondents for the newborn bloodspot consent is increasing, due to the additional birth defects, by 475 respondents resulting in a burden increase of 119 hours. The number of respondents for the online occupational questionnaire is increasing, due to the additional birth defects, by 40 respondents resulting in a burden increase of 14 hours. The addition of reportable infectious diseases information results in an increase of 648 hours. The number of respondents interviewed with the supplemental questionnaire is decreasing by 70 respondents, resulting in a burden decrease by 29 hours. The medical record review and request form that were not implemented is being removed from the ICR, resulting in a decrease of 357 hours. The net effect of all changes is an increase of 1,399 hours.

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

Data from the NBDPS and BD-STEPS are currently being analyzed and will continue to be analyzed. Data collection for the NBDPS is complete, and data collection for BD-STEPS began in February of 2014. The first coded and cleaned NBDPS dataset was released to the study Centers in October 2002 and the latest NBDPS dataset was released in March 2015. BD-STEPS data will be combined with NBDPS data for the questionnaire items that have remained the same and for the genetic data. The BD-STEPS dataset will include data from new and more detailed questions than NBDPS to allow for unique analyses that will include only BD-STEPS data. The first BD-STEPS dataset is anticipated to be released in 2019.

Online questionnaire data collection began in 2017. The medical record review was never implemented nor will it be in the future. The proposed reportable infectious diseases results data collection will begin in 2019.

For the purposes of analysis, individual defects will be categorized into appropriately homogeneous groups, including the presence of single and multiple defects. Analysis of risks from a given exposure will be carried out within broad categories, such as all vascular disruption defects, and be narrowed to a given defect such as Gastroschisis.

Because controls are population-based and randomly selected, all controls can be utilized for any of the subgroup analyses, which involve interview information. Additionally, other cases can be compared with the case group of interest in certain analyses, when appropriate.

The major analytic tool will be unconditional logistic regression. Relative risk estimates will first be made without consideration of potentially confounding variables. Important covariates such as maternal age and education will then be included.

An important analytic tool will be to look for evidence of gene-environment interaction in the analysis. Genetic information will be obtained using DNA-based polymorphisms. Individuals will be classified according to the presence or absence of specific susceptibility alleles, as well as whether they have those alleles in single (heterozygotes) or double dose (homozygotes). Evidence for interaction will be sought in logistic regression modeling using specific interaction terms.

The findings published from this study have and will continue to be published in medical journals and presented at scientific meetings. Information that may be useful in preventing birth defects will be adapted for health education materials. Over 300 manuscripts utilizing NBDPS pooled data and over 300 abstracts have been published to-date (**Attachment CC)**.

Table A.16-1 Project Time Schedule

Activity	**Time Schedule**
Data collection NBDPS maternal interviews	1998 – 2013
Data collection NBDPS cheek cells	1999 – 2013
Data collection BD-STEPS maternal interviews	2014 – Ongoing
Data collection of Newborn Bloodspots	2014 – Ongoing
Data collection from BD-STEPS online questionnaire	2017 – Ongoing

Data collection from BD-STEPS supplemental questionnaire (Stillbirth)	2018 – Ongoing
Reportable Infectious Diseases Results (new)	2019 (proposed) - Ongoing
Database coding (NBDPS and BD-STEPS)	2000 – Ongoing
Analysis (NBDPS and BD-STEPS)	Ongoing
Publication (NBDPS and BD-STEPS)	July 2000 – beyond end of study

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

Expiration dates are displayed, so no exemption is sought.

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

No exceptions are sought.