

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

Revision

Supporting Statement A

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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 ultimately to work to prevent major birth defects 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, some mothers will be asked to consent to medical records review 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 in the same population.
- **How data will be analyzed:**
Unconditional logistical regression will be the major analytic tool used for studying major defect groups and associated risk factors; relative risk estimates will first be calculated without consideration of potentially confounding variables, then important covariables such as maternal age and education will be included. We will also look for evidence of gene-environment interaction in analysis of NBDPS genetic data.

A. Justification

A.1. Circumstances Making the Collection of Information Necessary

This Information Collection Request is submitted under the classification “Revision.” The length of 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 the removal of the saliva collection protocol, the addition of incentives for previously planned bloodspot consent retrieval, and the implementation of an on-line questionnaire segment to the study.

The previously approved revision for this study (OMB # 0920-0010, expiration 01/31/2017) changed the title from the National Birth Defects Prevention Study (NBDPS) to the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS). Both the previous study, the NBDPS, and the new study, BD-STEPS, are conducted by the congressionally mandated Centers for Birth Defects Research and Prevention (CBDRP). Seven CBDRP are currently part of BD-STEPS: Arkansas (AR), California (CA), Iowa (IA), Massachusetts (MA), North Carolina (NC), New York (NY), and NCBDDD’s Division of Birth Defects and Developmental Disabilities (DBDDD).

Three changes have been determined necessary for BD-STEPS and are detailed in this revision request:

1. The originally planned BD-STEPS saliva collection has been discontinued because of budget constraints. The burden hours and cost estimates have been revised to remove saliva collection contact. The incentives for saliva collection were also removed from the payment descriptions.
2. In order to strengthen previously planned BD-STEPS bloodspot collection, additional follow-up and an additional incentive is proposed for inclusion in the request for bloodspot consent. Consent for bloodspots will be requested by five of the seven Centers and is expected to take less time than the collection of saliva that was previously planned. Burden hours and cost estimates have been revised to include these bloodspot collection changes.
3. In compliance with the BD-STEPS objective of exploring new data collection methods as stated in the FOA, the study proposes to implement a new on-line occupational questionnaire. BD-STEPS participants will be invited to participate in a 20-minute on-line questionnaire if they report selected occupations. All Centers will participate in this study section, and approximately one-third of participants are expected to report one of the selected occupations. Incentives are offered for completion of the on-line study. Burden hours and cost estimates have been revised to include this additional data collection.

In addition, although not a change, the medical record review that was part of the Supporting Statements previously did not include an associated burden estimate; this version adds burden estimates for this activity.

Background

Adverse reproductive outcomes such as birth defects and genetic diseases 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 have accounted for more than 139,000 hospital stays during a single year, resulting in \$2.6 billion in hospital costs. To put this in context, hospitalizations for all types of childhood cancer combined total approximately \$1.7 billion each year. 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. And, perhaps most importantly, folic acid dietary supplements can theoretically prevent up to half of all cases of fatal or permanently disabling neural tube defects such as anencephaly and spina bifida.

For the vast majority of the remaining birth defects, the causes are simply not known, and cases continue to occur. The existence of this continuing burden justifies reasonable attempts to reduce birth defects and genetic diseases. The first step in understanding and controlling adverse health outcomes is always surveillance for those outcomes by public health agencies. The CDC initiated birth defects surveillance in 1967, in the wake of the thalidomide disaster, with the Metropolitan Atlanta Congenital Defects Program (MACDP). MACDP has carried on this effort without a break since 1967, making it the longest running active surveillance system in the world.

Beginning in 1997, the State of Georgia exercised its option to require the reporting of birth defects under the state's disease reporting regulations, which list birth defects as a condition whose reporting is required by law. The Georgia Department of Community Health (DCH) authorized the CDC to serve as its agent in the collection of these case reports (authorization from the GA DCH is periodically renewed). **Attachment D** contains the MACDP authorization that will expire on 12/31/2018. All of the other BD-STEPS Centers have population-based birth defects surveillance systems that have legislative authority to collect information on infants with major congenital malformations. Since birth defects surveillance is a state requirement in all BD-STEPS Centers, the CDC is no longer requesting OMB clearance for population-based birth defects surveillance.

The Division of Birth Defects and Developmental Disabilities (DBDDD), however, obtained OMB clearance for the additional data collection that is carried out by the Centers for Birth Defects Research and Prevention (CBDRP). The CBDRP's National Birth Defects Prevention Study (NBDPS) transitioned to the CBDRP's Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS) in 2014; data collection for NBDPS began in 1997 and ended in 2013 (analysis of NBDPS data is ongoing), and BD-STEPS data collection began in 2014 (OMB # 0920-0010, expiration 01/31/2017 is included as **Attachment C**; approval for IRB Amendment

for change to BD-STEPS and the IRB annual approval are included as **Attachment E**). The previously approved OMB revision stipulated the end of NBDPS data collection and the beginning of BD-STEPS data collection.

In addition to surveillance, CDC has a long history of seeking to identify birth defects causes through the use of research studies. The CDC paired up the Birth Defect Risk Factor Surveillance study (BDRFS) with MACDP in 1993, following OMB approval (OMB 0920-0010; formerly titled Metro Atlanta Birth Defects and Factor Surveillance Program). The BDRFS collected additional information on exposure and susceptibility factors for cases of birth defects and for comparison controls. To help reduce birth defects among U.S. babies, in 1996 Congress directed the CDC to establish the 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 1996, CDC awarded cooperative agreements to 7 states (Arkansas (AR), California (CA), Iowa (IA), Massachusetts (MA), New Jersey (NJ), New York (NY), and Texas (TX)) to establish Centers for Birth Defects Research and Prevention (CBDRP). In September 2002, two additional states, North Carolina (NC) and Utah (UT), were funded and NJ did not receive continuation funding. From 2002 to 2013, a total of nine participating sites (AR, CA, IA, MA, NC, NY, TX, UT and the DBDDD, CDC in Atlanta) participated in the NBDPS. For the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS), seven Centers (AR, CA, IA, MA, NC, NY and the DBDDD, CDC in Atlanta) are participating. See **Attachment F** for current list of BD-STEPS Centers. One of the main activities for each Center will be to conduct BD-STEPS in their state (see section A.4).

With BD-STEPS as with NBDPS, infants with birth defects are identified through the birth defects surveillance system in each participating state; all of the CBDRP have population-based birth defects surveillance systems that have legislative authority to collect information on infants with major congenital malformations. Control-infants from each of the CBDRP will be selected randomly from live-born infants without a major birth defect, identified either from vital records (birth certificates) or from hospitals of birth, 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. Genetic samples were obtained for NBDPS, and will be obtained for BD-STEPS. In states that allow retrieval of blood spots, BD-STEPS participants will be 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-multiple siblings of this child.

This current change request is for the removal of the previously planned saliva collection from the BD-STEPS protocol, additional follow up, and the addition of a \$10 incentive for consent to retrieve newborn bloodspots for mothers of singletons and multiples and the addition of an on-line survey portion to the study. Saliva collection is no longer planned because of budget constraints.

Currently, OMB approval (OMB 0920-0010; expiration January 31, 2017) encompasses the data collected from six states and the DBDDD, CDC in Atlanta to conduct 275 interviews (200 cases and 75 controls) and an interview burden of 207 hours per Center per year. Reduction in the number of funded Centers (BD-STEPS Centers currently include AR, CA, IA, MA, NC, NY and the DBDDD, CDC in Atlanta) that were noted in the previously approved revision were made due to budget constraints. The removal of saliva collection noted in this revision was also made due to additional budget constraints.

Identification of Website(s) and Website Content Directed at Children Under 13 Years of Age
A website for this project will be located at www.bdsteps.org. The BD-STEPS website is not nor will it ever be directed at children under 13 years of age.

A.2. Purpose and Use of the Information Collection

I. How the Information will be Used and for What Purpose:

The purpose of BD-STEPS is to evaluate factors associated with the occurrence of birth defects and to test hypotheses for gene-environment interactions involved in the etiology of birth defects. Information collected in the interview (**Attachments G1 and G2**) 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 parental 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 DNA collected from the bloodspot samples will be used to study genetic susceptibility to the effects of environmental agents. For women with multiples (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.

BD-STEPS and its predecessor NBDPS have and 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 200 manuscripts have already been published using NBDPS data (see Section A.16), and many more manuscripts are proposed and currently being written. The information NBDPS and BD-STEPS provide is critical to the mission of the Public Health Service to reduce morbidity and mortality due to congenital malformations. Data from BD-STEPS and the NBDPS will play an important part in the decision-making process that determine federal research agendas, birth defect prevention activities, and the direction of funding programs such as cooperative agreements.

II. Impact of Proposed Collection on the Respondent's Privacy:

IIF is collected for this study, but privacy of the respondent is protected as detailed in section A.11. Because of these precautions, no impact on the respondent's privacy is anticipated as a result of participation in BD-STEPS data collection.

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

CATI Questionnaire (Attachments G1 and G2)

The interview questionnaire is administered as a computer assisted telephone interview (CATI). The average time to complete the interview is approximately 45 minutes. The BD-STEPS interview CATI 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 was pilot tested to ensure that the questions obtained the desired information and were sensitive to the circumstance surrounding the birth of a baby with a birth defect. When the study was changed from the BDRFS to the NBDPS, an expert panel reviewed the NBDPS questionnaire. Questions that did not appear to be yielding complete and accurate information were dropped or revised. Topics that provided limited data for analysis were also dropped. As with this previous transition, NBDPS questions that appeared to either consume large amounts of time or yield incomplete or possibly inaccurate information were dropped from the BD-STEPS CATI. These include illicit drugs, cold/flu, a general infectious disease question, and a food frequency questionnaire. Questions resulting in limited data for analysis as risk factors were also dropped: X-rays, scans, injuries, drinking water and surgeries.

A large portion of the BD-STEPS interview has been maintained from the NBDPS to make pooling of the CBDRP's NBDPS and BD-STEPS data possible; pooled data will facilitate the analysis of rare exposures and the examination of trends over time. The BD-STEPS interview retained topics include pregnancy history, family history, multiple births, fertility, maternal conditions and illnesses (including diabetes, genitourinary infections, and fevers), medication and herbal use, emotional stress, physical activity, obesity, alcohol and tobacco use, residential history, occupational history, and demographic characteristics (including race, ethnicity, acculturation status, and education).

Innovative questions were added to the BD-STEPS telephone interview in response to some of the findings from NBDPS and to new findings in the literature. Changes include:

- Adding questions about maternal diseases and their treatment including thyroid disease, asthma, autoimmune disease, transplant receipt, cancer, depression, and anxiety;
- Updating the instrument to evaluate possible new and emerging birth defects risk factors (e.g. new medications);
- Adding questions about exposures not explored before that have biological plausibility and public health importance (e.g. dental procedures and transplant receipt);
- Expanding sections to provide increased detail (e.g. indication and dose for specific medications).

The modified CATI is included in **Attachments G1 and G2**.

BD-STEPS is being conducted at seven locations around the country. The interview data from

the CDRPs will be used in statistical analyses by collaborators at each of the CDRP. Data will be released annually based on completed cohorts defined by expected date of delivery for each calendar year. There will be several data cleaning steps that will be implemented before release of the data.

On-Line Questionnaire

In order to query in-depth questions about maternal occupations, an on-line questionnaire has been developed. Participants are flagged in the CATI (**Attachments G1 and G2**) 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 CDRPs will send a standardized introductory email (one CDRP will send the invitation as a hard copy letter) to each participant; the introductory communication includes information about the online questionnaire, a link to the questionnaire, and the “log in” information. The on-line questionnaire will include 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 H1-H8**).

Medical Record Review

For a portion of participants reporting certain conditions, medical record reviews will be conducted with consent. Medical record review will both validate participant responses to questions about the care received as well as add detail to the answers received in the CATI.

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 the 17 selected birth defects (see **Attachment I** for a list of birth defects studied in the BD-STEPS) being conducted in the U.S. at this time.

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 is done by one central CDC-funded contract interviewing facility, which will increase consistency and efficiency over previous multiple site interviews. 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.

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 more research subjects to provide the necessary 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 more exposures for 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 February 18, 2015 (*Volume 80, Number 32, pages 8655-8656*). 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 made up of these collaborating scientists 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 in 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 J** 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. A \$20 money order was included in the introductory interview packet since this time. When the \$20 money order was added, participation rates for both cases and controls initially increased then stabilized between approximately 60 and 70%.

Because of funding constraints, the originally planned saliva data collection, that was part of the original OMB BD-STEPS revision, is no longer planned for BD-STEPS. No saliva collection kits will be mailed to participants, and therefore, the \$40 tokens of appreciation (two \$20 tokens) that were tied to this data collection will not be distributed. Although saliva collection and the associated incentives will no longer occur, the request for bloodspot consent that was originally planned (for states in which bloodspots can be shared and consent is needed) will now include a \$10 gift card.

In addition, a new online occupational questionnaire will be implemented for persons with certain occupations (see **Attachment H1-H8**) 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 will be mailed to the respondent.

The token of appreciation amount for both the online questionnaire and the bloodspot consent request is ten dollars. This amount is less than the \$20 gift card offered for the BD-STEPS CATI questionnaire and the two \$20 gift cards that were offered for saliva collection. The direct interviewer contact required for the CATI and the intensive nature of the saliva collection were determined to be more time-consuming than the newly proposed data collection steps. Based on this difference and the experience of the research group with previous studies, the BD-STEPS coordinating council voted to implement \$10 tokens of appreciation for the online questionnaire and bloodspot consent.

A.10. Assurance of Confidentiality Provided to the Respondents

The NCBDDD Privacy Act Officer reviewed this OMB application and has determined that the Privacy Act is applicable. A contractor will be used to conduct all interviews for the BD-STEPS Centers. Full names of respondents must be collected to enable the study purposes 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 (**Attachment K**, expiration February 2019).

The Certificate of Confidentiality, by preventing study staff from being forced under a court order or other legal action to identify study participants or provide individually identified data, 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 since they are assured their identity is secure and will not be subject to review by people outside of the research process (See interview telephone consent script, bloodspot retrieval written informed consents for mothers of singletons and multiples, medical record release and on-line questionnaire consent, in **Attachments L1/L2, M1/M2, N1/N2, O1/O2 and H1-8** respectively).

The data to be covered by 301(d) confidentiality certificate protection include the interviews, clinical data, 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 BD-STEPS Confidentiality and Data Use Oath (**Attachment P**).

IRB Approval

CDC IRB approval for the NBDPS and now BD-STEPS is renewed yearly; current approval expires January 29, 2016 (See **Attachment E** for current CDC IRB approval letter).

Privacy Impact Assessment

A Privacy Impact Assessment was done previously for this project in 2004, and a Certificate of Confidentiality was signed by Dr. Ron Otten on February 3, 2014 and will expire at the end of February of 2017. We provide a PIA overview below.

I. Overview of the Data Collection System

BD-STEPS data, are collected, like 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 45 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 G1/G2**. After the BD-STEPS CATI is completed, participants with certain occupations will be invited to complete a 20-minute on-line questionnaire (See **Attachment H1-H8**).

II. 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 (including medical record for participants with certain conditions), 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), medication use, environmental exposures. The on-line questionnaire, sent to a subset of participants, will also collect an occupational history including detailed questions about certain occupations (see **Attachment H1-H8**), and family demographics (i.e. infant birth place). In addition, the planned medical records review will request limited medical/medication information for persons with certain conditions to validate and expand on reported exposures.

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

As mentioned 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 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).

IV. Impact of proposed collection on the respondent's privacy

As mentioned previously in Section A2, IIF is collected for this study, but privacy of the respondent is protected as detailed in Section A.11. Because of study precautions, no impact on the respondent's privacy is anticipated as a result of participation in BD-STEPS data collection. Specimen collection consent forms also inform participants that all parts of the study are voluntary.

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

The participants are informed in three 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.

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

Consent will be obtained before collection of data. Initially, oral consent is obtained before the questionnaire administration is obtained. In addition, the online questionnaire contains a consent

page. There is a written consent for the Centers requesting bloodspots, and there is a medical record review release. See attached interview telephone consent script, bloodspot retrieval written informed consents for mothers of singletons and multiples, the on-line questionnaire consent, and the medical record review release in **Attachments L1/L2, M1/M2, N1/N2, H1-8 and O1/O2** respectively

VII. 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. 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.

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

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

A.11. Justification for Sensitive Questions

The maternal BD-STEPS interview asks questions about topics that may be considered sensitive: 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 question and answer sheet that is included in the initial mailing to mothers includes the following question and answer series: “*What if I don’t want to answer?* You may skip any questions you wish” and “*Do I have to participate?* No, there will be no harmful effects if you refuse. Your decision will not affect health care services or other benefits you or your family may receive.” (see Question and Answer sheet, **Attachment Q1/Q2**)

There is also a statement in the introductory letter that reads: “We will keep any identifying information that you provide during your interview confidential.” (see introductory letter, **Attachment R1/R2**).

The Human Subject Fact Sheet informs participants of the following (**Attachment S1/S2**):

“As a potential participant in this research study, you have the right to:

- * Be informed of the nature and purpose of the study.
- * Be given an explanation of the procedures to be followed in the study.

- * Be given a description of any discomforts and risks reasonably to be expected from the study procedures.
- * Be given an explanation of any benefits you can reasonably expect from participation.
- * Be informed of medical treatment, if any, available to you during and after the study if complications should arise.
- * Be given an opportunity to ask any questions concerning the study or procedures involved.
- * Be informed that you may withdraw from the study at any time without penalty.
- * Be given the opportunity to decide to participate or not without the use of any force or undue influence on your decision.

All information that we gather in this study will be kept confidential. This is because the study has been given a Certificate of Confidentiality by the Centers for Disease Control and Prevention. This means anything you tell us will not have to be given out to anyone, even if a court orders us to do so, unless you say it's okay. We may share information about you with other researchers but we will never use any names in reports or publications. You should also understand that study investigators are not prevented from reporting information obtained from you to authorities in order to prevent serious harm to yourself or others.

The BD-STEPS Question and Answer sheet will give you more information about how your privacy is protected in this study.

If you have questions about your rights as a subject in this research study, please call the Office of the Deputy Associate Director for Science for CDC at 1-800-584-8814, leave a message including your name, phone number, and refer to protocol #2087, and someone will call you back as soon as possible.”

The informed consent telephone script (**Attachment L1/L2**) 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 retrieval of previously collected infant bloodspots for singletons and multiples requires written informed consent (**Attachment M1/M2 and N1/N2**) in some states. Again, the participants are reminded in the written consent (**Attachments M1/M2 and N1/N2**) 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 consent and the medical record release (**Attachment O1/O2**).

Finally, 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 H1-H8**).

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

A.12. Estimates of Annualized Burden Hours and Costs

The interview is estimated to take approximately forty five minutes and is 15 minutes shorter than the previously OMB-approved NBDPS interview. The BD-STEPS interview is titled “Birth Defects Prevention Study: Computer Assisted Telephone Interview” (see **Attachment G1/G2**). Using the forty five minute estimate and a maximum of 1925 interviews planned annually (1,400 case mothers and 525 control mothers) a maximum interview burden of 1,444 hours for all Centers is estimated per year over three years. The forty five minute burden includes the time for the telephone consent script (**Attachment L1/L2**) 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 allow for bloodspot retrieval with participant consent. If a maximum of 1925 interviews would be expected for seven Centers, a maximum of 1375 would be expected for five Centers. A maximum of 15 minutes would be expected for the participant to read the bloodspot retrieval consent request, read and sign the consent form (**Attachment M1/M2 and N1/N2**). The anticipated maximum burden for bloodspot consent would be 344 hours annually.

With a maximum of 1925 interviews planned annually, and approximately one third of the respondents eligible for the on-line questionnaire (selected based on reporting occupations queried in the questionnaire), a maximum of 642 women would receive the on-line 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 214 hours annually.

We will conduct medical records review for medical conditions that affect approximately one fifth of the participants. Based on experience with consent forms, we expect the review, signing and mailing of the medical record release (**Attachment O1/O2**) to take a maximum of 15 minutes for participants. In addition, we expect the medical records reviewers will take approximately 30 minutes to identify, pull and send the requested records to the local study Centers.

The total annual burden hours for all activities for all individuals for all Centers is 2291 hours.

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 (Attach L1/L2)/BD-STEPS Computer Assisted Telephone Interview (Attach G1/G2)	1925	1	45/60	1444

Mothers (consent for bloodspot retrieval)	Written consent for bloodspot retrieval (Attach M1/M2 and N1/N2)	1375	1	15/60	344
Mothers (online occupational questionnaire)	Online Occupational Questionnaire (Attach H1-8)	642	1	20/60	214
Mothers (medical records release review)	Medical Record Request Form (Attachment O1/O2)	385	1	15/60	96
Records reviewers (medical records review)	N/A	385	1	30/60	193
TOTAL					2291

* These numbers are for the extreme situation that we would have complete participation. We expect ~70-75% participation for the interview

Table A.12-2 Estimated Annualized Burden Costs

Type of Respondents	No. of Respondents	No. Responses per Respondent	Avg. Burden per Response (in hours)	Total Burden Hours	*Hourly Wage Rate	Total Respondent Costs
Mothers (interview)	1925	1	45/60	1444	\$10.00	\$14,440
Mothers, (consent for bloodspot retrieval)	1375	1	15/60	344	\$10.00	\$3,440
Mothers (online occupational questionnaire)	642	1	20/60	214	\$10.00	\$2,140
Mothers (medical records release review)	385	1	15/60	96	\$10.00	\$960
Records reviewers (medical records review)	385	1	30/60	193	\$10.00	\$1,930
TOTAL						\$22,910

*Approximately 75% of women of child-bearing age do participate in the U.S. workforce (see <http://www.bls.gov/opub/ted/2000/feb/wk3/art03.htm>). A subset of these child-bearing 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 2014" located at http://www.bls.gov/oes/current/oes_nat.htm#00-0000<http://www.bls.gov/ncs/ocs/sp/ncbl0910.pdf>). 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 45 minutes, and an hour of respondent time is estimated to cost \$10. A maximum of 1925 are planned, 1400 cases and 525 controls, resulting in a maximum interview burden of 1444 hours for all Centers per year (\$14,440 per year).

Bloodspot consent costs: The anticipated maximum burden for bloodspot consent retrieval hours per year for the respondent mothers is 344 hours for all Centers per year (\$3,440 per year).

Online questionnaire costs: The anticipated maximum burden for online questionnaire completion per year for respondent mothers is 214 hours for all Centers per year (\$2,140 per year).

Medical records review costs: The anticipated maximum burden for medical record review per year for respondent mothers is 96 hours (\$960 per year) and medical records reviewers is 193 hours (\$ 1,930 per year).

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

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. NBDPS activities under Funding Opportunity Announcement #CDC-RFA-DD09-001 began on December 1, 2008 and ended on November 30, 2013. BD-STEPS FOA-DD-13-003 activities began in September, 2013. 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	.7	111,000
	Health Scientist, GS-14	.9	121,000
	Epidemiologist, GS-14	.6	80,000
	Medical Officer, GS-14	.5	92,000
	Health Scientist, GS-13	.6	76,000

Federal Government Other Direct Costs	Project Coordinator, GS-12	1	100,000
	Data Collection Supervisor, GS-13	1	135,000
	Printing		12,000
	Postage		5,000
	Office Supplies		5,000
	Travel		5,000
	Computer Equipment		3,000
Contractor Direct Labor	Programmer (contractor)	1	109,000
	Programmer Q&A (contractor)	.9	89,000
Interview contract	Total Interview contract costs		937,110
TOTAL COSTS			1,880,110

*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 details the removal of the saliva collection protocol, the addition of incentives for previously planned bloodspot consent retrieval, and the addition of an on-line questionnaire segment for a subset of the participants. In addition, this revision adds burden estimates for the medical records review that were previously included but did not yet have an associated burden estimate. These changes in combination slightly reduce the total expected burden hours for BD-STEPS data collection from the previous OMB approved data collection. In addition, as previously reported, the estimated burden for BD-STEPS (both for this revision and the initial BD-STEPS revision) is lower than the previously reported burden for NBDPS. This reduced estimate reflects fewer BD-STEPS Centers funded compared to NBDPS as well as a reduction in time for the BD-STEPS interview compared to the NBDPS interview. In addition, the change in specification for the BD-STEPS interview contract to include the conduct of interviews for all seven Centers will increase the estimate of annualized costs for the federal government.

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

Data from the NBDPS and BDRFS 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 also have some new and more detailed questions than NBDPS to allow for unique, analyses that will include only BD-STEPS data.

Online questionnaire data collection and the medical record review will begin in summer or fall of 2015.

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 covariables 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. Detectable relative risks using all controls have been calculated based on population exposure frequencies of 10% and 20%, with power (beta) set at 0.80 and significance level (alpha) set at 0.05. For the larger defect categories, after one year, detectable relative risks range between 2.7 and 3.9. However, for the rarer defects, detectable relative risks are quite high until 5-year data have accumulated.

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. 200 manuscripts utilizing NBDPS pooled data and over 300 abstracts have been published to-date (**Attachment T**).

Table A.16-1 Project Time Schedule

Activity	Time Schedule
Data collection NBDPS maternal interviews	1998 – 2013
Data collection BD-STEPS maternal interviews	2014 – Ongoing
Data collection NBDPS cheek cells	1999 – 2013
Data collection from BD-STEPS online questionnaire	2015 (proposed)
Medical record review	2015 (proposed)
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.