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

Revision

Supporting Statement A

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Table of Contents

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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 extension requested for OMB-PRA 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**).

Changes that are part of this revision include changing the project title from the National Birth Defects Prevention Study (OMB # 0920-0010, expiration 04/30/2015) to the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS). 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). Other changes included in this revision are the number of centers: nine CBDRP were part of the NBDPS data collection - Arkansas (AR), California (CA), Iowa (IA), Massachusetts (MA), North Carolina (NC), New York (NY), Texas (TX), Utah (UT) and NCBDDD's Division of Birth Defects and Developmental Disabilities (DBDDD); seven CBDRP will be part of BD-STEPS -AR, CA, IA, MA, NC, NY, and the DBDDD. Other revision changes include NBDPS questions that were removed and questions that were added to the BD-STEPS maternal interview. NBDPS questions that did not appear to be yielding complete and accurate information were dropped or revised. The protocol for participant contact has not changed for the two studies, but the participant materials (including consents) were changed slightly for BD-STEPS. Additional elements of this revision include that fact that for the BD-STEPS additional participant contact is planned in the future to request access for medical records for mothers who report certain medical procedures.

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 renewed on a yearly basis). **Attachment C** contains the MACDP authorization that will expire on 12/31/2013. 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, has OMB clearance for the additional data collection that is carried out by the Centers for Birth Defects Research and Prevention (CBDRP) under the National Birth Defects Prevention Study (NBDPS) (OMB # 0920-0010, expiration 04/30/2015), CDC Protocol # 2087, Expiration 1/29/2013 **Attachment D**; Approval for IRB Amendment for change to BD-STEPS **Attachment E**). We are currently seeking a revision to OMB clearance as NBDPS data collection ended in 2013 and BD-STEPS data collection will begin in 2014 (BD-STEPS Center grantees were named in August of 2013).

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, expiration 04/30/2015; 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. This 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) will participate. 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, control infants are randomly selected from electronic birth certificates or birth hospitals in the same population, and 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. After completing the interview, BD-STEPS participants will be sent a packet in the mail and asked to collect saliva samples from the mother, father, and infant. The collection kits with the saliva are then sent back by mail. For CBDRP in states that allow retrieval of blood spots, participants will be asked for permission to share a portion of the newborn blood spot for the child who is part of the study.

This request is for a Revision to the currently OMB approved project (OMB 0920-0010; expiration: April 30, 2015) and a title change from NBDPS to the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS). Currently, OMB approval (OMB 0920-0010; expiration: April 30, 2015) encompasses the data collected from all eight states (AR, CA, IA, MA, NC, NY, TX and UT) and by the DBDDD, CDC in Atlanta. These NBDPS data included 400 planned interviews (300 cases and 100 controls) and an interview burden of approximately 400 hours per Center per year. This current OMB revision (OMB 0920-0010; expiration: April 30, 2015) requests approval for 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 was made due to budget constraints.

1.1. Privacy Impact Assessment

A Privacy Impact Assessment was done previously for this project in 2004, and a Certificate of Confidentiality was signed by Dr. James Stephens (see Section A.10) on January 28, 2010 and will expire at the end of January of 2014. An application for renewal of this certificate will be submitted in 2013.We provide a PIA overview below.

I. Overview of the Data Collection System

BD-STEPS data, like NBDPS data will be collected by questionnaire using a computer assisted telephone interview (CATI). The average time to complete the BD-STEPS 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 G**.

II. Description of Information to be Collected

Using a computer assisted telephone interview (CATI) system, information in identifiable form (IIF) is collected, maintained and passed through the CDC database to facilitate the compilation of data for the CBDRP. Contact information for the subjects will be encrypted and sent from the individual CBDRP to the interviewing facility via the CDC provided secure SAMS (Secure Access Management Services) system. 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 biologic specimens (including saliva samples and in some centers, leftover newborn blood spots). 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, occupational history and family demographics (i.e. birth place).

III. 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 (**Attachment G**) 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 saliva samples will be used to study genetic susceptibility to the effects of environmental agents. 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 continuing 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 170 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

Questionnaire
The 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 will be 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 **Attachment G**.

BD-STEPS is being conducted at seven locations around the country. The interview data from the CBDRPs will be used in statistical analyses by collaborators at each of the CBDRP. 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.

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 H** 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 interviewing for all the sites will be done by one central CDC-funded contract interviewing facility, which will increase consistency and efficiency. 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 August 15, 2013 *(Volume 78, Number 158, pages 49758-49759).* One non-substantive public comment was received in response to this notice.

B. The principal investigators at each CBDRP currently work collaboratively with CDC scientists on scientific analysis and study conduct. BD-STEPS will have 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 will consist of the Principal Investigators in each of the study Centers and will have 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 I** 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 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%.

The NBDPS also provided tokens of appreciation to participants for the biologic sample collection portion of the study. The NBDPS cheek cell kits included $20 as an incentive to complete them and send them back. Overall, approximately 60% of participants completing the interview sent in a completed cheek cell kit. In June of 2002 as a pilot study, the NBDPS added an additional $20 incentive in two sites (New York and Atlanta) that was linked to the return of the cheek cell kits. Later, all NBDPS Centers implemented a total of $60 (three $20 incentives) for subjects who choose to complete the entire study including the return of the cheek cell samples. The third $20 money order was provided to any mother who returned samples for

herself and the baby or for just herself if the baby is deceased. While samples are requested from the father, the third incentive is not dependent on the cooperation of the father since this may pose a hardship to those mothers who are not in regular contact with the father.

Given the time and inconvenience required for the entire study (interview and biologics), a total of $60 is deemed an appropriate token of appreciation. Since the additional $20 money order increased the number of kits that were completed and returned to the Atlanta NBDPS Center, particularly among non-White women (Crider et al. "Racial and ethnic disparity in participation in DNA collection at the Atlanta site of the National Birth Defects Prevention Study."*Am J Epidemiology* 2006; 164(8):805-12), this incentive structure is deemed important for participant diversity. This 2006 study noted that among Black, Non-Hispanic women cheek cell participation increased from 31.7% to 46.0%. In the logistic model, the additional $20 money order was the only significant factor associated with increased participation among Black, Non-Hispanic women [OR=1.82, (95% CI, 1.22-2.78)]. Among Hispanic women, cheek cell participation increased from 36.6 to 45.6%. The third $20 money order, along with maternal education greater than 12 years and interview conducted in English were significant factors associated with cheek cell participation [OR 1.96(1.03-3.72), OR 2.14(1.13-4.07) and OR 3.00(1.56-5.78) respectively]. Although cheek cell participation among White, Non-Hispanic women increased from 60.7% to 62.7% upon implementation of the third $20 money order, this increase was not significant. Based on this research, all NBDPS collaborating centers used the three $20 incentive protocol, and to ensure the most racial and ethnic diverse participant pool for BD-STEPS, we remain committed to the same incentive structure. Anecdotal reports from the NBDPS interviews pointed out that not all women understood the value of the money orders. That is why we chose to change the format of the token of appreciation for BD-STEPS to chain-store gift cards to reduce the burden on the participants.

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 January 2010 (**Attachment J,** expiration January 2014).

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 and saliva collection written informed consent in **Attachments K and L** 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 M**).

IRB Approval

CDC IRB approval for the NBDPS and now BD-STEPS study is renewed yearly; current approval expires January 29, 2014 (See **Attachment D** for current CDC IRB approval letter). An IRB modification for BD-STEPS was received August 8, 2013 (**Attachment E**).

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. 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 N**)

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 O**).

The Human Subject Fact Sheet informs participants of the following (**Attachment P**):

"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 K**) 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 collection of saliva samples from the mother, father and infant requires written informed consent (**Attachment L**). Again the participants are reminded 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 explained again in the written consent.

The BD-STEPS interview data is compiled on a server at CDC. After the saliva samples have been collected, the saliva kits will be sent directly from each participant to their local Center

where they will be stored in a secure manner without identifiers (with the exception of study identification number) until they are shipped to the biorepository. The first 10 mother and baby samples that are collected from each Center will be sent from the Center to a laboratory (TBD) for DNA isolation and quality control before the DNA is shipped to the biorepository.

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 currently OMB-approved NBDPS interview. The BD-STEPS interview is titled "Birth Defects Prevention Study: Computer Assisted Telephone Interview, July 8, 2013" (see **Attachment G**). 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 K**) which is reviewed with the mother at the beginning of the call to collect the information via the CATI interview.

The collection of saliva kits for Biological Specimen Collection from the mother, father, and infant is estimated to take about 15 minutes per person. For the infant sample, the parent will rub long-handled sponges between the infant's cheek and gum; parents will be asked to swab a total of 5 sponges per infant. The infant's mother and father will be asked to provide their own saliva samples by spitting into a funnel connected to a small collection tube. Collection of the saliva samples takes approximately 2-5 minutes. The estimate of burden is 15 minutes per person to account for reading and understanding the written consent form (**Attachment L**) and specimen collection instructions (**Attachment Q and R**), collecting the specimens and mailing back the completed kits. The anticipated maximum burden for collection of the saliva collection is 1444 hours per year for mothers, fathers and infants combined (all centers).

The total annual burden hours for all activities for all individuals for all Centers is 2,888 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 K)/BD-STEPS Computer Assisted Telephone Interview (Attach G)	1925	1	45/60	1444
Mothers, fathers, infants (saliva samples)	Written informed consent for saliva collection (Attach L)/ Collecting saliva samples (Instructions (Attach Q and R))	5775	1	15/60	1444
TOTAL					2888

* These numbers are for the extreme situation that we would have complete participation. We expect ~70-75% participation for the interview and 60-70% participation for the saliva collection.

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)	1925	1	45/60	1444	$10.00	$14,440
Mothers, infants and fathers (saliva samples)	5775	1	15/60	1444	$10.00	$14,440
TOTAL						$28,888

***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, June 2006" located at 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 or biological specimen collection. A respondent father and infant can have time costs for the biologic specimen collection only. 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).

Saliva collection costs: The anticipated maximum burden for collection of the saliva is 1444 hours per year. Since one of the parents will have to collect the cheek cells from the infant, the hourly wage rate was applied to the infant's time burden so the total burden for the biologic specimen collection (for mother, father and infant) will be $14,440 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 will end 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 Scientists, GS-13	.6	76,000
	Project Coordinator, GS-12	1	100,000
	Data Collection Supervisor, GS-13	1	135,000
	Microbiologist GS–15	.5	80,000
Federal Government Other Direct Costs	Laboratory supplies		100,000
	Saliva kits		90,000
	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
	Data Manager (contractor)	.8	60,441
	Data Manager (contractor)	1	59,944
	Lab Project Coordinator (contractor)	.5	55,000
	Lab Technicians (contractor) 3	3.0	175,000
	Interview contract		306,456
Contractor Other Direct, Indirect Costs and Fees			978,159
	TOTAL COSTS		$2,848,000

*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

The estimated burden for BD-STEPS is lower than the previously reported burden for NBDPS. This reduced estimate has been changed to reflect 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 will begin 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 February of 2013. 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

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

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 BD-STEPS saliva samples	2014 – 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.