

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

**Supporting Statement A
Revision**

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November 9, 2022

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- **Goal of the study:** The purpose of the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS) is to evaluate factors associated with the occurrence of birth defects and stillbirths and ultimately to work to prevent major birth defects and stillbirths associated with maternal risk factors.
- **Intended use of the resulting data:** Data from BD-STEPS and the National Birth Defects Prevention Study (NBDPS) will play an important part in the decision-making process that determines federal research agendas, birth defect prevention activities, and the direction of funding programs such as cooperative agreements.
- **Methods to be used to collect:** Data will be collected via telephone interviews and online questionnaires. Some women will also be asked to consent for the use of: leftover newborn bloodspots, reportable infectious disease information, and fetal and/or placental specimens from stillbirths.
- **The subpopulation to be studied:** BD-STEPS includes interviews with women who had pregnancies affected by birth defects who are identified through the birth defects surveillance system in each participating state and women who experienced a stillbirth without a birth defect identified through fetal death records or hospital delivery records. Liveborn infants without birth defects (whose mothers will be invited for interview) serve as controls and are randomly selected from electronic birth certificates or birth hospitals for the same population as cases.
- **How data will be analyzed:** Univariate and bivariate statistics (e.g., percentages, Chi-squared tests) will be used to describe the distribution of potential risk factors among cases and controls. Logistic regression will be the primary analytic tool used for studying associations between categories of birth defects and potential risk factors; relative risk estimates will first be calculated without consideration of potentially confounding variables, then important covariates such as maternal age and education will be included. Other advanced statistical methods (e.g., machine learning, Bayesian analysis) will be used as appropriate. We will also look for evidence of gene-environment interaction in analysis of genetic data.

Birth Defects Study To Evaluate Pregnancy exposures

A. Justification

A.1. Circumstances Making the Collection of Information Necessary

Birth defects are associated with substantial morbidity and mortality in the United States. About one in every 33 babies is born with a birth defect. Birth defects are the leading cause of infant mortality -- 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 the National Center on Birth Defects and Developmental Disabilities (NCBDDD) at the Centers for Disease Control and Prevention (CDC).

For most birth defects, the causes are unknown, making prevention efforts challenging to develop. This continuing burden justifies reasonable attempts to reduce the prevalence of birth defects. To help reduce birth defects among U.S. babies, in 1996 Congress directed the CDC to establish Centers of Excellence for Birth Defects Research and Prevention. The mandate was formalized with passage of the Birth Defects Prevention Act of 1998 (see **Attachment A** for Public Law 105-168). This Act amended Section 317C of the Public Health Service Act (42 U.S.C. 247b-4) and authorized CDC to (1) collect, analyze, and make available data on birth defects; (2) operate regional centers that will conduct applied epidemiological research for the prevention of birth defects; and (3) provide the public with information on preventing birth defects.

In response to this mandate, the Division of Birth Defects & Infant Disorders (DBDID) at NCBDDD obtained OMB clearance for data collection that is carried out by the Centers for Birth Defects Research and Prevention (CBDRP). The CBDRP's first research effort was the National Birth Defects Prevention Study (NBDPS), which began data collection in 1997 and ended in 2013. The CBDRPs transitioned from NBDPS to the Birth Defects Study To Evaluate Pregnancy exposures (BD-STEPS), which began data collection in 2014. Seven CBDRP currently participate in BD-STEPS: Arkansas (AR), California (CA), Iowa (IA), Massachusetts (MA), North Carolina (NC), New York (NY), and CDC/NCBDDD's Division of Birth Defects & Infant Disorders (DBDID) which serves as the site of record for Georgia (GA). One of the main activities for each Center is to conduct BD-STEPS in their state (see section A.4).

Current OMB approval (OMB 0920-0010) expires February 28, 2023. The current BD-STEPS funding (2018-2023) will extend to another funding cycle (2023-2027), the intent of which is to continue to carry out the same BD-STEPS study design. We are currently seeking a revision to add two new consent forms. The length of data collection requested for OMB-PRA approval is 3 years.

A.2. Purpose and Use of the Information Collection

In BD-STEPS, pregnancies affected by birth defects (definitions provided in **Attachment J**) are identified through existing population-based birth defects surveillance systems in each participating state that has legislative authority to collect information on infants with major congenital malformations. Control infants are live-born infants without a major birth defect selected randomly from vital records (birth certificates) or from hospital birth logs and represent the birth population from which the case infants were identified. Mothers of case and control infants are mailed information about the study (**Attachments C2-C6**) and then interviewed by phone about their medical history, pregnancies, environmental exposures, and medications (questionnaire in **Attachment C1**). After completing the core interview, participants are also asked for permission to link to their reportable infectious disease history to better understand the role of infectious diseases (**Attachment D1-D3**). In states that allow retrieval of residual newborn blood spots, BD-STEPS participants with liveborn infants are asked for permission to share a portion of the newborn blood spot for the child who is part of the study, and for mothers of multiples, the co-siblings of this child (**Attachments E1-E5**). An online occupational questionnaire is sent to a subset of mothers in order to gather additional details about specific maternal occupations reported in the interview (**Attachment F1**). For two Centers, women who experienced a stillbirth (including those without major birth defects; definition provided in **Attachment K**) are also mailed additional information about the stillbirth-specific portion of the study (**Attachment G2**) and asked additional questions by phone (questionnaire in **Attachment G1**). A subset of women who experienced a stillbirth will be asked to authorize release of fetal and/or placental specimens for additional testing, to better understand the impact of SARS-CoV-2 acute infection in pregnancy on stillbirth, with special attention to the pathological findings that might contribute to our understanding of the mechanism (**Attachments G5-G6**).

Data from this information collection play an important part in the decision-making process that determines federal research agendas, birth defect prevention activities, stillbirth prevention activities, and the direction of funding programs such as cooperative agreements. The purpose of BD-STEPS is to identify modifiable maternal exposures in early pregnancy that may impact the risk for having a pregnancy affected by birth defects or stillbirth and to test hypotheses for gene-environment interactions involved in the etiology of birth defects. Information collected during the interview provides data for the evaluation of suspected new teratogens, mutagens, or environmental agents that are not prevalent enough to cause epidemics. For example, the information on family history of birth defects is useful in assessing the degree to which subsequent children in a family are at risk of having a birth defect or adverse outcome. The data gathered on maternal occupation is useful in assessing the impact of the workplace on reproductive outcome. The interviews also offer the possibility of identifying protective factors. The supplemental telephone interview allows for the identification of modifiable causes of stillbirth in infants with and without birth defects. The DNA extracted from the bloodspot samples will be used to study genetic susceptibility to the effects of environmental agents. Linkage to reportable infectious diseases will help assess the role of infections on birth defect risk. For women with multiple births (e.g., twins, triplets), collecting limited data and bloodspots from all liveborn 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. Lastly, the proposed change to collect fetal and/or placental specimens from stillbirths for additional testing will improve our understanding of the impact of SARS-CoV-2 acute infection in pregnancy on stillbirth.

Data from this information collection will continue to provide the nation with a source of information on potential causes of birth defects and stillbirths and will serve as a mechanism for identifying new substances in the environment that are harmful to fetal development. Over 350 manuscripts have already been published using NBDPS data (see Section A.16 and **Attachment N**), and many more manuscripts are proposed or are currently being written. The findings are interpreted with caution and all publications acknowledge the strengths and limitations of the study design. The

information provided is critical to the mission of the Public Health Service to reduce morbidity and mortality due to congenital malformations.

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

BD-STEPS participants are recruited to complete an interview questionnaire that is administered in English or Spanish using a computer assisted telephone interview (CATI). The average time to complete the core interview is approximately 55 minutes (**Attachments C1**); the supplemental stillbirth interview is 25 minutes (**Attachments G1**). The BD-STEPS CATI is designed to ascertain only information that is pertinent and useful in identifying possible risk factors associated with adverse reproductive outcomes. The CATI has extensive question skip logic that eliminates duplicative responses in order to reduce burden on participants. The CATI makes it possible to complete the interview in segments so that participants have the option of completing the interview in several sessions rather than all at once. Standard data elements, such as demographic information, that are available from an existing source, either a birth/death certificate or hospital records, are not collected during the telephone interview to reduce the burden on participants.

To advance the use of information technology and reduce burden on participants, an online occupational questionnaire was developed in order to query in-depth questions about maternal occupations. Participants who report one of eight specific occupational areas of interest in the initial interview (agriculture, cosmetology, electronic equipment operator, healthcare, janitorial, office worker, restaurant, and teaching) are then recruited to complete an online questionnaire. A standardized introductory email includes information about the online questionnaire and a link to the questionnaire. The online questionnaire, which is available in English or Spanish, includes occupation-specific questions and an informed consent page. (The eight occupation-specific questionnaires including the introductory communication and the informed consent page is included as **Attachments F1.1-F1.8**). While the majority (76%) of participants thus far have completed the questionnaire online, if the online questionnaire is unavailable or a participant chooses not to complete the online questionnaire, a paper questionnaire is mailed to the participant. The questions on the paper questionnaire are the same as those on the online version. Other methods used to reduce burden on participants include the use of a “quick response” or “QR” code on communication

materials to allow participants to easily store interview contact numbers to better recognize phone calls when the interviewer is trying to reach them.

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

Efforts to identify duplication include periodic systematic reviews of the scientific literature and frequent discussions with birth defects researchers at federal agencies and research institutions across the United States as facilitated by Center and CDC contacts. BD-STEPS is the only population-based case-control study of risk factors for the 22 selected birth defects (see **Attachment J** for a list of birth defects and case definitions studied in the BD-STEPS) being conducted in the U.S. at this time. BD-STEPS is also conducting research on risk factors for stillbirths, including those without major birth defects (see **Attachment K** for the definition). The questionnaire is included as **Attachment G1**.

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

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

number of birth defects risk factors for which information is included in the surveillance system, as well as to identify unusual patterns of birth defect occurrences, but do not have sufficient samples of rare birth defects or detailed exposure assessments that the BD-STEPS case-control study contributes.

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

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

A.6. Consequences of Collecting the Information Less Frequently

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

There are no legal obstacles to reduce the burden.

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

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

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

A. A copy of the agency's 60-day Federal Register Notice is attached (60-day Federal Register Notice **Attachment B**). The notice, as required by 5 CFR 1320.8 (d), was published on March 1, 2022 (*Volume 87, Number 40, pages 11442-11444*). Two public comments were received and replied to; see 1) and 2) below.

1. PUBLIC COMMENT

From: Jean Public <jeanpublic1@yahoo.com>

Sent: Monday, March 7, 2022 5:28 PM

To: OMB-Comments (CDC) <omb@cdc.gov>; mercola@gmail.com; info@nja9cv.org;

sue@njaicv.org; JOHN GILMORE <jgilmore@autismactionnetwork.org>; info@icandecide.org

Subject: Fw: pregnancy and alleged birth defects - from vaccines? public comment on federal register this agency should not get a penny of American tax dollars for this research. This agency deserves a minus for its work on health. This agency cannot be trusted on the subject of birth defects. This agency is dealing with harm from vaccines which can cause early birth defects in newborns. The clinical trial and lack of safety in pushing vaccines over the last 40 years shows a clear propensity for vaccines to cause defects for babies and children. Their safety in clinical trials was lacking. This agency has a vested interest in trying to defend itself by trying to say its birth defects and not the horrible vaccines that have been pushed on children. Babies that are making them have defects.

Also is this agency anti-American. I note few Americans have jobs at this agency. Why is that. Is there an anti-American bent at this agency? Why would that be?

Pregnancy is a very delicate time where mothers to be have been told since time immemorial to be careful what you put in your body. Yet these money-maker pals with big pharma push vaccines into expectant mothers and into their newborn babies, all can have massive effects in these delicate times. Clearly, safety is being ignored.

It is time we make this agency smaller or put it out of business and start over. I do not think the ethics, morality, conflict of interest that is present is helping this agency to truly help the health and safety of the American people. I do not support this project at all.

This agency has crossed the line. This comment is for the public record please receipt. Ejan Publicee

jean public1@yahoo.com

1. RESPONSE

Thank you for your comment. The Birth Defects Study to Evaluate Pregnancy exposureS (BD-STEPS) will provide researchers with more knowledge about what factors might raise or lower the risk of having a baby with a birth defect. Certain vaccines are safe and recommended for women before, during, and after pregnancy to help keep them and their babies healthy. This study provides important clues to help us in our journey to ensure that every child is born with the best possible health.

2. PUBLIC COMMENT
PUBLIC SUBMISSION

As of: 6/7/22 11:08 AM

Received: April 16, 2022

Status: Pending_Post

Tracking No. l22-cnzh-86zj

Comments Due: May 02, 2022

Submission Type: Web

Docket: CDC-2022-0030

Birth Defects Study To Evaluate Pregnancy
exposureS (BD-STEPS)

Comment On: CDC-2022-0030-0001

Birth Defects Study To Evaluate Pregnancy
exposureS (BD-STEPS) 2022-04191

Document: CDC-2022-0030-DRAFT-0002

Comment from Clime-Coates, Laura

Submitter Information

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General Comment

This comment responds to Docket No. CDC–2022– 0030, Extension to the Birth Defects Study to Evaluate Pregnancy exposureS (BD–STEPS), (OMB Control No. 0920–0010, Exp. 2/ 28/2023)— National Center on Birth Defects and Developmental Disabilities (NCBDDD) at the Centers for Disease Control and Prevention (CDC). The information gathered from continuance of this study is important for many reasons, including increasing understanding of birth defects and stillbirths to continue to work towards prevention, further examination of findings from the National Birth Defects Prevention Study (NBDPS), and monitoring changes over time (2021).

Stillbirth numbers are higher in the U.S. than in other countries with similar development and economic characteristics, and numbers of stillbirths have fallen in those countries, while the U.S. has plateaued, leading experts to recommend further research in this area (Gregory,2014; Lawn, 2016). The April 2021 BD-STEPS protocol published by the CDC states that: “...stillbirths [are] a largely under-studied perinatal outcome despite being one of the most common adverse pregnancy outcomes, accounting for one-half of all perinatal deaths. To study risk factors for stillbirths with and without birth defects, this study will utilize population-based, active surveillance systems of stillbirths to identify novel modifiable pregnancy exposures that decrease the occurrence of stillbirths, with a particular focus on maternal medication use [and] perception of decreased fetal

movement.”

The CDC website lists the following groups as working with the CDC to understand and prevent stillbirths: NCBDDD, National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) Division of Reproductive Health, and the National Center for Health Statistics (NCHS) (2022). Coordinating with the CDC’s NCBDDD on the BD-STEPS study are the Centers for Birth Defects Research and Prevention (CBDRP) and specific university and public health department centers designated as part of the study (2021). The CDC website states that there is still much to be learned in the areas of birth defects and stillbirth, and that stillbirth needs to be considered a public health issue in order to raise awareness, work towards prevention strategies, increase training for health care providers, and make grief counseling more accessible (2022). The CDC–2022– 0030, extension to the BD-STEPS, has plans to incorporate the study of stillbirth, stating: "The etiology and preventable causes for stillbirths are largely unknown. To better understand stillbirths, mothers of stillbirths without major birth defects will be included in the study... Each CBDRP will interview approximately 100 eligible stillbirth cases with no birth defects each year for inclusion in the study..." I believe the continued collection of data on both birth defects and stillbirths are a vital function of the CDC and the practical utilities of the study include raising public awareness, increasing health care provider awareness and training, increasing maternal awareness and modifying behaviors and medication use, and providing grieving parents counseling after pregnancy loss or diagnosis of birth defect. Researchers are studying the effects of pregnancy loss and stillbirth on women, noting the importance of each of the elements listed above, especially grief and trauma training for health care providers, and increasing public/maternal awareness (DeMontigny, 2017; Edmond, 2019; Freidenfelds, 2021). As a woman who has endured multiple reproductive losses, and as a graduate student pursuing research to improve women’s reproductive experiences, I strongly support extending the BD-STEPS research.

2. RESPONSE

Thank you for your comment and support. The goal of BD-STEPS is to provide researchers with more knowledge about what factors might raise or lower the risk of having a baby with a birth defect as well as stillbirths with and without birth defects. This study provides important clues to help us in our journey to ensure that every child is born with the best possible health.

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

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

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

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

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

upon completing the telephone interview, in addition to the \$20 gift card included in the introductory packet.

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

- Prepaid incentives yield higher response rates than promised incentives or no incentives
- Monetary incentives yield higher response rates than gifts
- Response rates increase with increasing amounts of money, though not always linearly
- Effect of incentives has not changed over time, although baseline response rates have dropped substantially
- References:
 - Singer E, Ye C. “The use and effects of incentives in surveys” *The ANNALS of the American Academy of Political and Social Sciences*; 2013; 112-141.
 - Cantor D, O’Hare BC, and O’Connor KS. “The use of monetary incentives to reduce nonresponse in random digit dial telephone surveys” *Advances in Telephone Survey Methodology* 2008; 471-498.
 - Edwards P, et al. “Increasing response rates to postal questionnaires: systematic review” *BMJ* 2002; 324(7347):1183.
 - Church AH. “Estimating the effect of incentives on mail survey response rates: A meta-analysis” *Public Opinion Quarterly* 1993; 57(1):62-79.
 - Singer E, et al. “The effect of incentives in interviewer-mediated surveys. *Journal of Official Statistics* 1999; 15(2):217-230.

Focus groups were conducted to assess factors related to participation in the biologics components of NBDPS (buccal cell collection) among mothers who participated in the NBDPS interview.

Participants reported that monetary incentives increased perceived study legitimacy.

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

For the infectious disease linkage consent request, a \$10 gift card will be sent to mothers, with a thank you letter, as a token of appreciation after a signed consent form is returned or verbal consent is obtained (see **Attachments D2-D4**).

For the newborn bloodspot consent request, a \$10 gift card will be sent to mothers, with a thank you letter, as a token of appreciation after a signed consent form is returned or verbal consent is obtained (see **Attachments E2-E6**). Centers that do not retain newborn bloodspots or that do not need written consent, do not make this request.

The online occupational questionnaire is offered to participants who reported certain occupations during the interview to ask more in-depth questions about potential exposures in the workplace (**Attachment F1**). If the BD-STEPS online occupational questionnaire is completed, a \$10 gift card is mailed to the respondent with the thank you letter (**Attachment F2**).

For the two Centers participating in the stillbirth component of BD-STEPS (AR and MA), a \$20 gift card is sent to mothers as part of the thank you letter for this part of the study (**Attachment G4**).

With this revision, we are planning to invite a subset of women from these two Centers to participate in a COVID-19-related sub-study. Women who experienced a stillbirth between January 1, 2017 and October 31, 2019 who have a record of placental and fetal tissue samples available for testing, regardless of prior participation in the BD-STEPS interview, will be sent an introductory letter (**Attachment G5**) and form asking for written authorization to have these samples shipped to CDC for additional COVID-19-related testing (**Attachment G6**). A \$10 gift card will be also included as a token of appreciation.

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

The NCBDDD Privacy Act Officer reviewed this OMB application and has determined that the Privacy Act is applicable. A contractor is used to conduct all interviews for the BD-STEPS Centers. Full names of respondents must be collected to enable the study goals to be achieved. Records will be covered under the CDC Privacy Act system of records 09-20-0136, Epidemiologic Studies and

Surveillance of Disease Problems. BD-STEPS is based on the previous experience of the NBDPS and Birth Defects Risk Factor Study (BDRFS), which were 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 in February 2014. BD-STEPS continues to maintain a Certificate of Confidentiality, but a hard-copy of a Certificate is no longer issued by CDC due to changes in Section 301(d) of the Public Health Service Act (PHS) Act, which authorizes the use of Certificates, that was amended by the 21st Century Cures Act. The amended Act states that the Secretary of HHS shall issue Certificates to persons engaged in biomedical, behavioral, clinical, or other research activities in which identifiable, sensitive information is collected. Due to this change, CDC-supported research started or ongoing after December 13, 2016, and in which identifiable, sensitive information is collected, is protected by a Certificate. Researchers conducting research with a Certificate are required to protect the privacy of research subjects in accordance with Section 301(d) of the PHS Act. Language referring to Certificates was included in the terms and conditions for this funding - Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS) II RFA-DD-18-001.

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

The data to be covered by 301(d) confidentiality certificate protection include the BD-STEPS interviews/questionnaires (phone and online), clinical data, infectious disease information collected, and results of testing on biological samples. 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 identifiable study information is limited to a very small number of authorized study personnel. All personnel with access to study data must take the CBDRP Confidentiality training and sign the CBDRP Confidentiality Acknowledgement (**Attachment L**).

Privacy Impact Assessment

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

As described in Section A8.B, 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 aggregate data from participant specimens will be analyzed as part of NIH-funded future studies, and the NIH Genomic Data Sharing (GDS) policy requires data from NIH-supported genomic studies be deposited into NIH data repositories, including the database of Genotypes and Phenotypes (dbGaP).

II. Overview of the Data Collection System

BD-STEPS data are collected, as NBDPS data were, in part by questionnaire using a CATI. The average time to complete the core BD-STEPS CATI is estimated to be 55 minutes where the NBDPS CATI lasted one hour. The average time to complete the stillbirth CATI is estimated to be 25 minutes. The interviews used in BD-STEPS are 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 C1** for core interviews, **Attachment G1** for supplemental stillbirth interviews. After the BD-STEPS CATI is completed, participants with certain occupations are invited to complete a 20-minute online questionnaire (See **Attachment F1**).

III. Description of Information to be Collected

Contact information (phone numbers and mailing addresses) for the subjects is collected through existing surveillance programs at individual CBDRP, encrypted, and sent from the individual CBDRP to the interviewing facility via the CDC-provided Secure Access Management Services (SAMS) system. Maternal telephone interviews are administered by staff at the interviewing facility using a CATI system, and information in identifiable form (IIF) is collected, maintained and passed through the CDC-developed database to facilitate the compilation of data for the CBDRP. The following are all categories of IIF collected: name, date of birth of mother, father, and baby, mailing address, phone numbers, email addresses, medical information and notes, and genetic data derived from leftover newborn bloodspots (for singletons and multiple births). Other categories of non-IIF data include pregnancy history (e.g., number of previous pregnancies and fertility treatments), maternal conditions and illnesses (e.g., diabetes, high blood pressure and infections), family history, lifestyle and behavioral factors (e.g., stress, alcohol use, and marijuana use), medication use, environmental exposures, travel history, and stillbirth-specific information (e.g., fetal movement, maternal sleep position). The online occupational questionnaire, sent to a subset of participants, collects detailed information about certain occupations (see **Attachment F1**). In addition, the linkage to reportable infectious diseases data includes a consent request for release of these data by the state health department.

A Privacy Impact Assessment was signed by Jarell Oshodi on June 12, 2020. We provide a PIA overview below (see **Attachment M1** for signed *Privacy Impact Assessment Form* and M2 for explanation of why the signature is not visible on the form).

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

According to the guidance provided, participants receive the Privacy Act Statement as it pertains to this information collection (see **Attachment C5**). The participants are informed in several places before the interview takes place that participation is voluntary: the question and answer sheet and the human subjects fact sheet that are mailed to the mother before the interview, and the informed

consent telephone script that is read to the mother before the interview (**Attachments C3, C4, C7**). See Section A11 for more information on the emphasis of the voluntary nature of participation.

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

Consent is obtained before collection of data. Oral consent is obtained before the CATI questionnaire is administered. For subjects eligible for the online questionnaire, the first page of the online (and hard copy, if requested) questionnaire contains the consent and participants must indicate consent to proceed with the survey. For Centers requesting bloodspots, written or verbal consent is obtained prior to accessing bloodspots. Written or verbal consent is obtained prior to the release of reportable infectious diseases information from the state health department. For subjects eligible for the two-part telephone interview, verbal consent is obtained before the CATI questionnaire is administered.

VI. How the information will be secured

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

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

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

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

IRB Approval

CDC IRB approval for the NBDPS and now BD-STEPS is renewed yearly; the most recent IRB approval occurred on August 19, 2022 (See **Attachment I** for current CDC IRB approval letter) and

current approval expires January 29, 2023 (See **Attachment H** for 2022 continuation CDC IRB approval letter).

The maternal BD-STEPS interview asks questions about topics that may be considered sensitive, including alcohol use, pregnancy history, history of sexually transmitted diseases, history of depression and anxiety, and use of fertility medications and procedures. These topics are included in the study because several reports have linked these factors to birth defects and/or stillbirths, 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 human subjects fact sheet (**Attachment C3**) and the question and answer sheet (**Attachment C4**) that are mailed to the mother before the interview, and the informed consent telephone script that is read to the mother before the core interview (**Attachment C7**).

The informed consent telephone script for the core interview (**Attachment C7**) 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. Similarly, the telephone informed consent script for the supplemental stillbirth interview (**Attachment G3**) also explains that the mother can choose not to answer any specific question and that answers will be kept confidential.

The online questionnaire includes a one-page informed consent. This consent, like the verbal 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 F1**).

Written and verbal informed consent is also obtained for release of previously collected reportable infectious disease information from each state's National Electronic Diseases Surveillance System (**Attachment D2-D3**). Again, the participants are reminded in the consent that all parts of the study are voluntary and all data gathered in the study are stored without names attached. The protection

afforded by the Certificate of Confidentiality is also explained again in the written and verbal consent for the release of reportable infectious diseases results. Along with the infectious disease consent form, participants will receive an infectious disease frequently asked questions that provides additional information on access to and results of requested information among other questions (**Attachment D1**).

Written informed consent is obtained for retrieval of previously collected newborn bloodspots for singletons and multiples in some states while some states obtain verbal informed consent for newborn bloodspots for singletons and multiples (**Attachment E2-E5**). Again, the participants are reminded in the consent that all parts of the study are voluntary and all data gathered in the study are stored without names attached. The protection afforded by the Certificate of Confidentiality is also explained again in the written and verbal consent for the release of newborn bloodspots. Along with the newborn bloodspot consent form, participants will receive a newborn bloodspot frequently asked questions that provides additional information on access to and results of requested information among other questions (**Attachment E1**).

Finally, the written consent for authorized release of fetal and/or placental specimens for additional COVID-19-related testing notes that women are not required to participate in this component of the study (**Attachment G5-G6**).

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

A.12. Estimates of Annualized Burden Hours and Costs

The core interview is estimated to take approximately 55 minutes. The BD-STEPS core interview is titled “Birth Defects Prevention Study: Computer Assisted Telephone Interview” (see **Attachment C1**). For the five Centers not participating in the stillbirth component of the study, a maximum of 370 interviews are planned per year per center, 270 cases and 100 controls; for the two Centers participating in additional stillbirth interviews, 590 interviews are planned per Center, 270 cases with birth defects, 100 controls, and 220 stillbirths without birth defects. With seven Centers and a maximum of 3,030 interviews, the maximum interview burden for all centers combined would be

2,778 hours per year over three years. The 55-minute burden includes the time for the telephone consent script (**Attachment C7**) which is reviewed with the mother at the beginning of the call to collect the information via the CATI.

With a maximum of 2,590 interviews planned annually (not including stillbirths without birth defects), and approximately one third of the respondents eligible for the online questionnaire (selected based on reporting occupations queried in the questionnaire), a maximum of 830 women would receive the online questionnaire (**Attachment F1**). Completion of the online questionnaire is estimated to take 20 minutes including reading introductory communication. The anticipated maximum burden for the online questionnaire is 277 hours annually.

For women from the two Centers participating in the stillbirth component of BD-STEPS, mothers of infants with or without birth defects that are stillborn and controls are asked to participate in a second part of the telephone interview (**Attachment G1**). The 25-minute second part of the interview includes the time for informed consent. Based on a maximum of 640 women to be interviewed with the two-part questionnaire, the maximum burden time would be 267 hours annually. The 25-minute burden includes the time for the telephone consent script (**Attachment G3**) which is reviewed with the mother at the beginning of the call to collect the information via the supplemental interview.

We will request the release of reportable infectious diseases information from all women who complete the CATI. Of the 2,590 interviews planned annually, a maximum of 2,590 women would receive the infectious disease consent request. Based on experience with consent forms, we expect the review, signing and mailing of the release of reportable infectious diseases information (**Attachment D2 and D3**) to take a maximum of 15 minutes for participants. The anticipated maximum burden for the reportable infectious diseases information is 648 hours annually.

Five of the seven BD-STEPS Centers request consent for retrieval of leftover newborn bloodspots. If a maximum of 2,590 interviews would be expected for seven Centers, a maximum of 1,850 would be expected for the five Centers requesting consent for retrieval of leftover newborn bloodspots

(excluding stillbirths, for which newborn bloodspots are not available). A maximum of 15 minutes would be expected for the participant to read the bloodspot retrieval consent request and sign the consent form (**Attachments E2-E5**). The anticipated maximum burden for bloodspot consent would be 463 hours annually.

A subset of women from the two Centers participating in the stillbirth component of BD-STEPS will be invited to participate in a COVID-19-related sub-study. We anticipate 157 women to meet inclusion criteria. Based on experience with consent forms, we expect the review, signing and mailing of the consent form (**Attachment G6**) to take a maximum of 15 minutes for participants. The anticipated maximum burden for these consent forms is 40 hours annually.

The total estimates of annual burden hours for all activities for all individuals for all Centers is 4,473 hours. The estimates of annualized burden hours represent the total population however due to lower participation rates (no more than 60%), the actual burden will be lower as well.

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

Respondents	Form Name	Number of Respondents*	Number of responses per respondent	Avg. burden per response (In hours)	Total Burden Hours
Mothers (interview)	Core Computer Assisted Telephone Interview (Attachment C1)	3,030	1	55/60	2,778
Mothers (infectious disease consent)	Linkage to Reportable Infectious Disease Consent (Attachments D2 and D3)	2,590	1	15/60	648
Mothers (consent for residual newborn bloodspot retrieval)	Residual Newborn Bloodspot Consent (Attachments E2-E5)	1,850	1	15/60	463
Mothers (online questionnaire)	Online Occupational Questionnaire (Attachment F1)	830	1	20/60	277
Mothers of all AR/MA stillbirths and controls (interview)	Supplemental Computer Assisted Telephone Interview (Attachment G1)	640	1	25/60	267
Mothers of	Authorization Form for	157	1	15/60	40

AR/MA stillbirths with specimens available for testing	Stillbirth COVID-19 Sub-Study (Attachment G6)				
TOTAL					4,473

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

Table A.12-2 Estimated Annualized Burden Costs

Type of Respondents	No. of Respondents	No. Responses per Respondent	Avg. Burden per Response (in hours)	Total Burden Hours	*Hourly Wage Rate	Total Respondent Costs
Mothers (interview)	3,030	1	55/60	2,778	\$14.00	\$38,892
Mothers (infectious disease consent)	2,590	1	15/60	648	\$14.00	\$9,072
Mothers (consent for residual newborn bloodspot retrieval)	1,850	1	15/60	463	\$14.00	\$6,482
Mothers (online questionnaire)	830	1	20/60	277	\$14.00	\$3,878
Mothers of all AR/MA stillbirths and controls (interview)	640	1	25/60	267	\$14.00	\$3,738
Mothers of AR/MA stillbirths with specimens available for testing	157	1	15/60	40	\$14.00	\$560
TOTAL						\$62,622

*Approximately 72% of women of childbearing age do participate in the U.S. workforce, of which one-fifth are part-time workers (<https://www.bls.gov/opub/reports/womens-databook/2020/home.htm#:~:text=the%20technical%20notes.>), Selected%20demographic%20characteristics,previous%20year%20(69.1%20percent)). 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 2021" located at http://www.bls.gov/oes/current/oes_nat.htm). We have thus calculated an average hourly wage rate of \$14.00 for the respondents for this ICR.

Interview costs: A respondent mother can have time costs for the interview. An interview is estimated to take 55 minutes, and an hour of respondent time is estimated to cost \$14. A maximum of 3,030 are planned, resulting in a maximum interview burden of 2,778 hours for all Centers per year (\$38,892 per year).

Infectious disease records review costs: The anticipated maximum burden for notifiable infectious disease record review per year for respondent mothers is 648 hours (\$9,072 per year).

Bloodspot consent costs for five Centers: The anticipated maximum burden for bloodspot consent retrieval hours per year for the respondent mothers is 463 hours for all Centers per year (\$6,482 per year).

Online questionnaire costs: The anticipated maximum burden for online questionnaire completion per year for respondent mothers is 277 hours for all Centers per year (\$3,878 per year).

Supplemental telephone interview cost for mothers of stillbirths and controls for two Centers: The anticipated maximum burden per year for respondent mothers is 267 hours (\$3,738 per year).

Authorization Form for Stillbirth COVID-19 Sub-Study: The anticipated maximum burden per year for respondent mothers is 40 hours (\$560 per year).

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

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

A.14. Annualized Costs to the Federal Government

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

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

	CDC and Contract Personnel*	FTEs	Costs* (dollars)
Federal Government Personnel Costs	Epidemiologist, GS-15	.05	12,575
	Health Scientist, GS-14	.8	180,358
	Health Scientist, GS-14	.8	165,099
	Medical Officer, GS-14	.8	194,940
	Health Scientist, GS-13	.9	146,310
	Health Scientist, GS-13	.8	114,200
	Data Manager, GS-13	1	193,357
	Data Programmer, GS-14	.25	29,958
Federal Government Other Direct Costs	Printing		5,000
	Postage		3,000
	Office Supplies		3,000
	Travel		6,000
	Computer Equipment		2,000
Contractor Direct Labor	ORISE	1	87,174
	ORISE	1	82,942
	Project Coordinator	1	155,462
	Medical Officer	.5	99,690
	Medical Officer	1	158,316
	Epidemiologist	.8	151,818
Interview contract**	Total Interview contract costs		2,034,677
TOTAL COSTS			3,825,876

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

**Interview contract cost is all inclusive and includes on-site study coordinator and data manager.

A.15. Explanation for Program Changes or Adjustments

The total estimates of annual burden hours for all activities for all individuals for all Centers is 4,473 hours, which is an increased of 40 hours from the burden shown in the current inventory (4,433 hours). This increase is due to our revision to invite a subset of women from two Centers to participate in a COVID-19-related sub-study (see consents included in **Attachment G6**).

We are also requesting a non-substantive change to the core CATI (**Attachment C1**). In this request, we proposed to modify questions in the core CATI to gather additional details about COVID-19 infections and vaccinations. New questions will gather information on COVID-19 infections diagnosed using an at-home test, repeat infections, and the level of treatment received for each infection. We also proposed to gather information on booster doses of COVID-19 vaccine. The

previous version of the CATI has COVID-19-related infection questions that only ask about the occurrence of one infection that was diagnosed by a doctor or other healthcare provider and the vaccination questions only ask about the primary series of COVID-19 vaccinations. Details of the non-substantive change are provided in **Attachment O**.

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

Data from the NBDPS and BD-STEPS are currently being analyzed and will continue to be analyzed. Data collection for the NBDPS is complete, and data collection for BD-STEPS began in February of 2014. The first coded and cleaned NBDPS dataset was released to the study Centers in October 2002 and the latest NBDPS dataset was released in March 2015. BD-STEPS data will be combined with NBDPS data for the questionnaire items that have remained the same and for the genetic data. The BD-STEPS dataset will include data from new and more detailed questions than NBDPS to allow for unique analyses that will include only BD-STEPS data. The first BD-STEPS dataset was released in 2019. The latest BD-STEPS dataset was released in August 2021.

Online questionnaire data collection began in 2017. The reportable infectious diseases results began data collection in 2019.

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

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

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

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

The findings published from this study have and will continue to be published in medical journals and presented at scientific meetings. Information that may be useful in preventing birth defects will be adapted for health education materials. Over 350 manuscripts utilizing NBDPS pooled data and over 300 abstracts have been published to-date (**Attachment N**).

Table A.16-1 Project Time Schedule

Activity	Time Schedule
Data collection NBDPS maternal interviews	1998 – 2013
Data collection NBDPS cheek cells	1999 – 2013
Data collection BD-STEPS maternal interviews	2014 – Ongoing
Data collection of Newborn Bloodspots	2014 – Ongoing
Data collection from BD-STEPS online questionnaire	2017 – Ongoing
Data collection from BD-STEPS two-part questionnaire (Stillbirth)	2018 – Ongoing
Reportable Infectious Diseases Results	2020 – 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.