

**Centers for Birth Defects Research and Prevention  
Birth Defects Study To Evaluate Pregnancy exposures (BD-STEPS)**

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**Centers for Birth Defects Research and Prevention (CBDRP)**  
**Birth Defects Study To Evaluate Pregnancy exposureS Protocol**

**1. GENERAL DESCRIPTION AND OVERVIEW**

Birth defects are the leading cause of infant mortality in the United States, accounting for 20% of all infant deaths in 2007 (1). In addition, birth defects contribute substantially to childhood morbidity and long-term disability. Although several human teratogens have been identified, for most infants with birth defects, the etiology is unknown. Surveillance systems can be used to identify some birth defects risk factors for which information is included in the surveillance system, as well as to identify unusual patterns of birth defect occurrences. A number of case-control studies of birth defects have been conducted, 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 defects.

The Centers for Birth Defects Research and Prevention (CBDRP) is a collaborative effort between the U.S. Centers for Disease Control and Prevention's (CDC's) National Center on Birth Defects and Developmental Disabilities (NCBDDD) and a number of other Centers located within universities or public health departments across the United States with access to data from birth defects surveillance registries. This collaborative effort provides a unique and unprecedented opportunity to evaluate risk factors for individual birth defects. Major strengths include: 1) large population-based birth defects surveillance systems including diverse populations and diverse environments; 2) detailed, standardized case definitions (classifying

birth defects into subgroups that are as etiologically and pathogenetically homogeneous as possible) and specified criteria for case inclusion; 3) an interview instrument that is uniformly administered allows collection of information on relevant exposures and potential confounders; 4) large sample size that provides unprecedented power to evaluate potential risk factors for specific birth defects; and 5) the use of biologic markers for exposure and genetic susceptibility. For births from October 1997 through December 2011, the CDRP collaborated on the National Birth Defects Prevention Study (NBDPS), a case-control study of risk factors for birth defects (2). Beginning with births in January 2014, the CDRP will collaborate on a case-control study called the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS), which will extend and expand upon NBDPS.

#### **1.A. Executive Summary**

As with NBDPS, the purpose of BD-STEPS is to identify modifiable maternal exposures in early pregnancy that may increase the risk for having a pregnancy affected by certain major, structural birth defects. BD-STEPS retains many important parts of NBDPS and also makes some changes that build upon experience from NBDPS and other collaborative projects of the CDRP, namely the Birth Defects Risk Factor Surveillance (BDRFS) project (2, 3). As with NBDPS, collaborators in the BD-STEPS study sites will use data from existing population-based birth defects surveillance systems to identify children with major birth defects; BD-STEPS will include a subset of the 30 major birth defects included in NBDPS, focusing on 17 defects. As with NBDPS, mothers of the case infants and mothers of randomly selected live born control infants will be contacted and invited to participate in a maternal interview covering multiple topics. The BD-STEPS interview will focus on the key areas of: (1) diabetes, obesity, and physical

activity; (2) other chronic maternal medical conditions; (3) infertility; and (4) medication use.

Similar to NBDPS, after the interview, mothers may receive kits to collect saliva specimens from herself, her child (if living), and the child's father to use for genetic and epigenetic analyses. The saliva sample section of BD-STEPS depends on availability of funds and will not initiate at study onset. From some sites, consent will be requested for residual dried bloodspots from newborn screening. In contrast to NBDPS, consent will be requested to access certain medical records for purposes of future validation research. Another distinction is that BD-STEPS will have seven Collaborating Centers; NBDPS most recently had nine. BD-STEPS will start data collection for infants with a date of birth, or pregnancy termination, on or after January 1, 2014 in each of the defined study regions.

### **1.B. History of CDC-Sponsored Birth Defects Case-Control Studies**

The Atlanta Birth Defects Risk Factor Surveillance (BDRFS) project, which was initiated in 1993, was a surveillance-based approach to evaluating risk factors for birth defects (CDC Protocol #1104, OMB #0920-0010). BDRFS was conducted on the foundation of the Metropolitan Atlanta Congenital Defects Program (MACDP) (CDC Protocol #1955), which has been in existence since 1968. MACDP is a population-based, multiple-source-case-ascertainment, birth defects surveillance system for the metropolitan Atlanta area. In 1993, CDC funded two five-year cooperative agreements with Iowa and California to conduct the BDRFS using their own surveillance systems. Among the three participating sites, 1,995 interviews were completed (1,213 case mothers and 782 control mothers). Several specific analyses have been published and substantial experience was gained during the five-year BDRFS effort (4 6).

In 1998, Congress passed legislation, the Birth Defects Prevention Act of 1998 (Attachment 1) that directed CDC to establish the Centers for Birth Defects Research and Prevention (CBDRP). Money was appropriated in 1996 for CDC to initiate some of the activities described in the bill, which included the funding of the CBDRP.

Cooperative agreements for a period of five years were awarded to five states in 1997 (California, Iowa, Massachusetts, New York, and Texas) to establish the CBDRP and support their collaboration in activities aimed at the prevention of birth defects. Data collection included births occurring on or after October 1, 1997. Two additional sites were funded in 1998 (Arkansas and New Jersey); data collection at these sites began January 1, 1998. Specifically, these awards were designed to: 1) bolster ongoing surveillance activities (including the integration of prenatal diagnoses into surveillance registries); 2) develop, implement, and evaluate local studies (including research, linkage to special services, and program evaluation); and 3) contribute 400 interviews per year (300 case interviews and 100 control interviews) to the National Birth Defects Prevention Study (NBDPS). A competitive renewal process for additional five-year cooperative agreements occurred in June of 2002. Two new Centers, North Carolina and Utah, received funding as a result of this re-competition. The North Carolina and Utah Centers began data collection in the fall of 2003. Data collection for the new Centers included births occurring after December 31, 2002. Two Centers (New York and New Jersey) did not receive continued funding in June of 2002. New Jersey did not resume new data collection; the New York Center received full funding again in September 2004 and began collecting new data. Another competitive renewal process for an additional 5 years occurred in December 2008; five centers were funded in December 2008 (Arkansas, California, Massachusetts, North

Carolina, and Utah), and 3 centers (Iowa, New York and Texas) were funded in June 2009 after a 6 month break in funding. An Atlanta site, operated by staff at CDC, also functioned as a Center for the entire NBDPS data collection period. Data collection for the NBDPS was halted for infants with estimated dates of delivery on or after January 1, 2012, and all NBDPS interviewing was halted on March 31, 2013. NBDPS conducted interviews with 43,838 women, including 32,042 mothers of infants with birth defects and 11,796 mothers of infants without birth defects. Specimens have been collected from 25,265 women, including 19,019 mothers of infants with birth defects and 6,246 mothers of infants without birth defects.

### **1.C. Certificate of Confidentiality**

The CDBRP has had a Certificate of Confidentiality for the NBDPS since August 2, 1999 (Attachment 2). This Certificate of Confidentiality was renewed in February 2014, with an expiration date of February 28, 2019. The Certificate specifies that only investigators who are part of the CDBRP collaboration may access individual level data from NBDPS and BD-STEPS that include Personally Identifiable Information or PII (e.g. date of birth of mother and baby). Potential participants will be given the following information about the Certificate of Confidentiality (or something very similar):

We will keep any identifying information that you provide during your interview confidential. This is assured by a Certificate of Confidentiality that protects your legal rights under the Public Health Service Act (*under section 301[d] of the Public Service Act 42 U.S.C. 241[d]*). The Certificate of Confidentiality prevents study staff from being forced under a court order or other legal action to identify you or anyone else in this study. This protection lasts forever (even after death) for any persons who were

subjects in the research during any time the certificate was in effect. However, you should understand that the investigators are not prevented from reporting information obtained from you to authorities in order to prevent serious harm to yourself or others. Records may be reviewed by officials checking on the quality of the research. Information about you may be shared with other researchers when and if it has been approved by research review committees. We will never use any names in reports or publications.

#### **1.D. Institutional Review**

The original CDC Institutional Review Board (IRB) approval for the Atlanta BDRFS was granted on May 14, 1992, with the original authorization to give an Assurance of Confidentiality granted on May 8, 1992. The most recent CDC IRB approval for NBDPS was granted on December 30, 2013 with an expiration date of January 29, 2015. All CBDRP that collaborate on BD-STEPS will have cooperative agreements with CDC (with the exception of the CDC site for the CBDRP) and local IRBs will defer to a central study IRB held by the CDC IRB, consistent with current recommendations (7), unless prohibited by state law or the Center's own Institutional Review Board. Once grantees have been identified, documents supporting internal and external reviews and approvals will be submitted to the appropriate IRB(s). This deferral is new for BD-STEPS as Centers that participated in NBDPS obtained IRB approval from local Centers' institutional review boards.

## 2. INVESTIGATORS AND COLLABORATORS

### 2.A. CDC Investigators

#### 2.A.1. CDC's Centers for Birth Defects Research and Prevention (CBDRP)

This activity involves collaboration between the National Center on Birth Defects and Developmental Disabilities (NCBDDD) of the CDC, and the state-based CBDRP. Jennita Reefhuis, PhD, Birth Defects Epidemiology Team, is the Project Officer for the CBDRP and Kimberly Newsome, MPH, BSN, is the Study Coordinator. Dr. Reefhuis and Ms. Newsome are primarily responsible for the direction and administration of the CBDRP. As project officer, Dr. Reefhuis is responsible for directing and providing technical assistance to the CBDRP in developing the BD-STEPS protocol, evaluating study conduct, and overseeing the individual cooperative agreements with the CBDRP. Dr. Reefhuis is responsible for insuring that all IRB and OMB requirements are met. In addition, Dr. Reefhuis is the lead scientific consultant to BD-STEPS. Dr. Reefhuis has responsibility for providing technical assistance to the CBDRP including study design, protocol development, data storage, and data management. As study coordinator, Ms. Newsome is responsible for the day-to-day management of the study, coordination of activities among the Centers, and preparation and submission of all CDC IRB, OMB and Certificate of Confidentiality applications.

Data Manager/Programmer, Chris Cosper and a contracted programmer are responsible for security, transfer and maintenance of BD-STEPS-related databases. They also design, program, and implement custom applications to assist in the execution of the study. In addition, they

support, instruct, and coordinate the data pooling efforts of CDC contractors and data managers from the CDRP.

Mary Jenkins, PhD is responsible for coordinating the biologics component of BD-STEPS. Dr. Jenkins is responsible for overseeing the collection, storage and analysis of biologic specimens for CDC local BD-STEPS and all study sites of BD-STEPS.

Richard Olney, MD, MPH is responsible for providing technical assistance related to case definition and birth defect classification and for clinical review of potential BD-STEPS participants.

The BD-STEPS central laboratory has not yet been determined.

#### **2.A.2. CDC Site for BD-STEPS**

As Principal Investigator of the Atlanta BD-STEPS site, Sarah Tinker, PhD, MPH is responsible for the study protocol, study conduct, interview instrument, and scientific aspects of the study design, data management, and analysis. In addition, Dr. Tinker is responsible for meeting human subjects' requirements, supervising the activities of the CDC BD-STEPS staff, and collaborating with the other CDRP.

Dr. Mary Jenkins is responsible for the collection, storage and analysis of biologic specimens for the CDC site for the CDRP. She is responsible for coordinating the efforts between the NCBDDD and the BD-STEPS Central Lab (to be determined). Richard Olney, MD MPH, determines the eligibility of all of the cases included in the CDC site of BD-STEPS and collaborates with the clinicians at all of the CDRP.

Dr. Jan Cragan, MD, MPH has primary responsibility for MACDP and its related projects. The local Data Manager and Local Study Manager share responsibilities for record management and coordination of the CDC BD-STEPS study, including case identification and data entry.

In addition to the above investigators, there may be a variety of other CDC investigators involved at any one time with this surveillance and research project. Some of these include:

i) The National Center on Birth Defects and Developmental Disabilities:

Elizabeth Ailes, PhD

Fernando Arena, MD, PhD

Cheryl Broussard, PhD

Tiffany Colarusso, MD

Krista Crider, PhD

April Dawson, MPH

Ridgely Fisk-Green, PhD

Jaime Frias, MD

Amanda Garcia, MPH

Suzanne Gilboa, PhD

Margaret Honein, PhD, MPH

Jodi Jackson, PhD

Kara Polen, MPH

Hilda Razzaghi, PhD

Matthew Oster, MD, MPH

Regina Simeone, MPH

Jill Glidewell, MPH, MSN

Clinton Alverson, MS

Meghan Frey, MPH

As CDRP collaborators, all CDC investigators/administrators listed here worked previously on NBDPS and will continue to work on BD-STEPS.

## **2.B. External CDRP Investigators**

The principal investigators at each of the CDRP work collaboratively with CDC scientists on scientific aspects of study design and analysis, including development of the study protocol, interview instrument design, and study conduct. In addition, they are responsible for: 1) meeting human subjects research and IRB requirements; 2) data storage and management; 3) providing clinical review of potential cases; 4) tracking and tracing of study subjects and mailing study materials; 5) statistical aspects of study design and analysis, and 6) sample storage, management, and analysis for BD-STEPS samples requested from the biorepository. Principal Investigators at each CDRP are the following:

### **2.B.1. Arkansas**

Arkansas Children's Hospital Research Institute

Charlotte A. Hobbs, MD, PhD  
Principal Investigator  
13 Children's Way, Slot 512-40  
Little Rock, AR 72202

### **2.B.2. California**

Stanford University

Gary Shaw, DrPH  
Principal Investigator  
Stanford University  
1265 Welch Road  
Stanford, CA 94305-5415

**2.B.3. Iowa**

The University of Iowa

Paul Romitti, PhD  
Principal Investigator  
105 River Street  
S416 CPHB  
Iowa City, IA 52242-5000

**2.B.4. Massachusetts**

Commonwealth of Massachusetts Department of Public Health

Marlene Anderka, ScD, MPH  
Principal Investigator  
Massachusetts Dept of Public Health  
250 Washington Street, 5th Floor  
Boston, MA 02108-4603

**2.B.5. North Carolina**

University of North Carolina, Chapel Hill

Andy Olshan, PhD  
Co-Principal Investigator  
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Chapel Hill, NC 27599-7435

**2.B.6. New York**

New York State Department of Health

Marilyn Browne, PhD  
Principal Investigator  
Empire State Plaza- Corning Tower  
Room 1203  
Albany, NY 12237-0000

## 2.C. Other Collaborators

In an effort to further understand birth defects risk factors, there may be a variety of additional investigators involved at any one time with this study. Such collaboration is essential to the success of this project because it allows scientists with differing expertise to work together, substantially improving the ability to better understand birth defects risk factors.

In addition to the collaborators from the CDRP, a number of individuals employed by the interviewing contractor will have important roles in this project as they will be conducting interviews of all study subjects. This contracted organization will have specific responsibilities, including: 1) maintaining the interview instrument; 2) interviewing study subjects; 3) ensuring a functional link between the BD-STEPS workflow system and the contact information files and any of their call center electronic tracking systems; 4) providing monthly reports on the number of interviews and other metrics; 5) making follow-up and reminder calls to study subjects for collection of biologic specimens; and 6) providing complete, clean, and edited data in a timely fashion. The interviewing contractor will also provide the coding of interview data. Primary

Personnel (Abt Associates Inc.):

Gabriella Newes-Adeyi, PhD, MPH  
Abt Associates Inc.  
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Cathy Murphy  
Abt Associates Inc.  
5001 South Miami Boulevard  
Central Park West, Suite 210  
Durham, NC 27703-8062  
(919) 294-7752

#### **2.D. BD-STEPS Coordinating Council**

The Principal Investigators from each of the CBDRP, including the CDC site, will comprise the BD-STEPS Coordinating Council. The Coordinating Council is the decision-making body for BD-STEPS. They will meet monthly by conference call and at least once per year in person.

#### **2.E. BD-STEPS Data Sharing Committee**

Each of the CBDRP will provide two members for the Data Sharing Committee. This committee will review letters of intent, proposals, abstracts, and manuscripts that involve previously unpublished data collected by BD-STEPS. The data covered by these guidelines include all interview, clinical, and biologic data associated with this study.

### **3. SUBJECT IDENTIFICATION AND RECRUITMENT**

#### **3.A. Case Identification**

##### **3.A.1. Birth Defects Surveillance**

All of the CBDRP have population-based birth defects surveillance systems that have legislative authority to collect information on infants with major congenital malformations. A description of the surveillance system in each state can be found in Attachment 3 (A copy of the document providing this authority to CDC for Atlanta is included in Attachment 4). Each program monitors all births occurring to residents in a defined geographic area having between 30,000 and 80,000 births each year. These birth defects surveillance programs include information on live born and stillborn infants diagnosed with at least one major birth defect within the first year of life, with diagnoses ascertained up to 18 months of life. Similar methods of multiple source case ascertainment are used at each site; most cases are registered through regular visits to local hospitals by members of the CBDRP surveillance staff, where records such as log books and patients' charts in nurseries, maternity units, and pediatric wards are reviewed to obtain clinical information and basic demographic data. Cases are also identified from the records of local cytogenetic laboratories, prenatal diagnosis clinics, genetic clinics, and vital records. Certificates of live birth, infant death, and stillbirth are supplied by state health departments.

Data are abstracted at each of the CBDRP onto a local surveillance case record, which has been designed to meet specific surveillance needs at the site. However, all BD-STEPS case records include the same basic demographic information, specific written diagnoses, six-digit diagnostic codes, birth related information, cytogenetic data, complications of birth, prenatal data, pregnancy history, family history and other risk factor information.

The use of prenatal diagnosis for birth defects has become increasingly prevalent over the past decade. In many instances, because of a diagnosis during pregnancy of a serious birth defect or chromosomal abnormality, the pregnancy is electively terminated. For surveillance systems to have complete population-based ascertainment of birth defects, it is now necessary to obtain information from prenatal diagnostic clinics on elective terminations of pregnancy. It is important to include prenatally diagnosed cases in any epidemiologic study of birth defects; without such inclusion criteria, an increasingly substantial number of case-infants will not be included in the study, which will likely make interpretation of study results very difficult. All CBDRP plan to include prenatally diagnosed cases for which the pregnancy ended in termination, to the fullest extent possible.

### **3.A.2. Case Definition**

Infants are eligible for inclusion in BD-STEPS if they have one or more defects from the list of 17 birth defects included in Attachment 5. In addition to selecting birth defects with unknown or uncertain etiology, these defects were selected for the following reasons. The defect is:

- a) Considered to be a major defect (affecting survival, requiring substantial medical care, or resulting in marked physiological or psychological impairment);
- b) Usually identifiable in the first six weeks of life (may be extended for some defects); and
- c) Consistently ascertainable and classifiable.

In addition, other criteria considered when developing the list included:

- a) The defect is common (and thus of public health importance);

- b) The pathogenetic mechanism of the specific defect is similar to other included defects; or
- c) There are specific etiologic hypothesis(es) which require additional study.

Cases can be: 1) live born infants; 2) stillborn infants greater than 20 weeks gestational age or 500 grams; or 3) prenatally diagnosed and terminated fetuses at any gestational age or weight.

### 3.A.3. Eligibility Clinical Review

Clinical staff at each of the CBDRP will review the abstracted medical records of case-infants which are ascertained by that CBDRP to determine if that case-infant meets the specified case definition and inclusion criteria. The clinicians use a standard clinical review and classification protocol that is based on the NBDPS clinical criteria (8). To evaluate case eligibility, the clinicians use a system of case-notes in the clinical database shared between the CBDRP, which allows questions and issues to be rapidly resolved. Phone conferences and meetings for the clinicians involved in the study will be scheduled as needed.

Clinical inclusion and exclusion criteria include:

- 1) Certain types of birth defects cases which have been ascertained solely through prenatal diagnosis will be included (including the method of diagnosis, as noted by clinical reviewer);
- 2) Cardiac defects will be included if the diagnosis is based on echocardiography (at least);
- 3) Cases with the following known etiology will be excluded: chromosome imbalance (karyotype, microarray), and Mendelian gene disorders; and

- 4) Cases with teratogenic syndromes and recognized phenotypes of unknown or uncertain etiology will be included.

### **3.B. Control Identification**

Control-infants from each of the CBDRP will be selected randomly from live-born infants without a major birth defect, identified either from vital records (birth certificates) or from hospitals of birth, and represent the birth population from which the case infants were identified. Using birth certificates to identify controls is only an option in states where vital records are recorded electronically in a timely manner (generally within weeks of delivery).

The CBDRP that use birth certificates as their primary method for the selection of controls are:

- 1) Iowa: access to these certificates is obtained through a signed research agreement with the Iowa Department of Public Health;
- 2) Massachusetts: access to these certificates is obtained through data access review according to state laws, and IRB review as needed;
- 3) Georgia: as an agent for the Georgia Department of Human Resources, CDC has legal authority for the collection of health information, as provided in Chapter 12 of the Official Code of Georgia (OCGA). With this authority, CDC routinely reviews medical records of births in a three-county metropolitan Atlanta area to determine if birth defects are present and to abstract information, as necessary to conduct the Metropolitan Atlanta Congenital Defects Program. In addition to having this authority, the protocol for selecting controls in this manner has been in place since the beginning

of BDRFS in 1993 (CDC protocol #1104). Original IRB approval of this method was granted on May 14, 1992 and the most recent approval of protocol #2087 was granted on December 30, 2013 (exp. January 29, 2015). All BD-STEPS controls will be selected from vital records as long as access remains timely.

- 4) North Carolina: authority, through the NC Birth Defects Monitoring Program within the NC DHHS, is to sample from birth certificates and take personal identifiers.
- 5) Arkansas: The Arkansas Center uses a random sample of the state's birth certificates for control selection. The Arkansas Center has a formal Memorandum of Understanding (updated in 2012) with the Arkansas Department of Health to access vital records information. Additional authority to access these pregnancy-related data was established by the 1985 legislation act for the state's birth defect surveillance system. On a monthly basis, the Health Department selects and delivers a random sample of newly processed birth certificates to serve as potential controls for the Center's research studies.

The CBDRP which use hospital data for the selection of controls are:

- 1) New York: Control infants will be randomly selected from the New York State Statewide Planning and Research Cooperative System (SPARCS) files of births to women resident in the study area. SPARCS records are hospital discharge records;
- 2) California: has a legal mandate to obtain information on infants without malformations to serve as controls;

- 3) Georgia: If vital records data are not readily available, uses the CDC's control selection protocol to select controls from hospital records.

In anticipation of a 70% participation rate (based on the experience from the NBDPS), each of the CDRP will select randomly from the population (from either vital records or hospital birth logs) approximately 100 eligible controls each year for inclusion in the study.

Whether hospital records or birth certificates are used as the source for control-infants, the records are reviewed to ensure that, given the available information, the selected control-infant does not have a birth defect. Records are also reviewed to abstract information for the purpose of follow up and contact.

### **3.C. Exclusion Criteria for Cases and Controls**

There are certain criteria for both case and control mothers that result in ineligibility to participate in BD-STEPS. Case and control infants are not eligible if:

- 1) The mother is not a resident of the geographic area covered by one of the CDRP population-based registries at the time of delivery;
- 2) The mother is deceased;
- 3) The mother is incarcerated;
- 4) The mother participated previously in the NBDPS or BD-STEPS;
- 5) The mother cannot complete the interview in either English or Spanish;
- 6) The mother is younger than 15 (or younger than 18 if required by law); or
- 7) The infant is adopted or in foster care.

### **3.D. Tracking Database**

#### **3.D.1. Data Flow**

The BD-STEPS workflow system will facilitate the flow of information on eligible participants.

Access to the data will be limited; sites will only have access to their own data. The workflow will only have the study-id number. The central interviewing site will have access to the contact information for all of the sites after appropriate agreements between the contracting facility and the local sites are in place.

### **3.E. Recruitment**

#### **3.E.1. Initial Mailing and Incentive**

A letter of introduction (Attachment 6) is mailed to prospective participants by the local site after a participant has been identified, and at least six weeks after the estimated date of delivery. Included with the letter of introduction are a \$20 gift card, a fact sheet on rights of human subjects (Attachment 7), a calendar (Attachment 8), a question and answer sheet (Attachment 9), and a medicine summary sheet (Attachment 10).

#### **3.E.2. Tracking and Tracing**

Address information from the data abstraction or vital records is used for the initial mailing.

After 4-10 days, the interviewers start calling the available phone numbers (see Figure 1) to contact the mother for interview. Interview initiation is allowed up to 18 months after Estimated Date of Delivery or EDD. If no confirmation is received that the available numbers reach the intended woman, an additional request for contact information is sent to the mother's address from the local center (Attachments 11 and 12). The central interviewing

facility will also use online tracing providers to find additional contact information. Follow up calls, letters and emails are used to locate hard to reach women (Attachments 13-16).

**3.E.3 Scheduling interviews**

When the woman is reached by the central interviewing facility, an interview can be completed at that time or scheduled for a later time. Interviewing will be available at a range of hours and during both weekdays and weekends. Women can also call the toll-free number to arrange for an interview after they receive the intro packet or email the interviewing facility to schedule an interview.

#### **4. INTERVIEW**

##### **4.A. Centralized Interviewing Staff**

BD-STEPS interviewing for all the sites will be done by one central CDC-funded contract interviewing facility, which will increase consistency and efficiency. 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. When possible, interviews will be conducted via the telephone using a system that allows eligible participants to see a local phone number displayed on their caller ID display for each of the sites (Voice over Internet Protocol, VoIP).

##### **4.B. Interview**

###### **4.B.1. Oral Consent for Interview**

For the interview, no written informed consent will be obtained. Oral consent to an interview is obtained prior to conducting the interview (See telephone script, Attachment 17). In case of a mother who is an un-emancipated minor the interview will be postponed until she is 18, if possible, and otherwise consent will be asked of the maternal grandmother of the infant. Any questions a woman may have about the study are answered, and verification of the study may be obtained, if necessary, from the Principal Investigator at each CBDRP site.

###### **4.B.2. Interview Instrument**

Mothers of all case and control infants who agree to participate in BD-STEPS are interviewed by telephone. This interview provides the framework for BD-STEPS, providing critical information, which is used in all aspects of the study. Building on interviews of over 40,000 mothers of infants with and without birth defects from the NBDPS (OMB 0920-0010; expires 1/31/2017;

amendment for BD-STEPS interview instrument approved January 3, 2014), an approximately 45-minute computer assisted telephone interview (CATI) will be programmed for BD-STEPS (Attachment 18). The primary language of the BD-STEPS interview instrument is English. However, the interview has been translated to Spanish (12% of NBDPS interviews were completed in Spanish). In addition, letters of correspondence, telephone scripts and consent forms have been translated for Spanish-speaking participants. Being able to complete the interview in English or Spanish is a criterion for inclusion in the study.

#### **4.B.3. Questions Retained from NBDPS**

A large portion of the BD-STEPS interview will be maintained from the NBDPS to make pooling of the CDBRP'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 instrument contains sections on 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).

#### **4.B.3. Innovative Questions Introduced in BD-STEPS**

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 additional 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).

#### **4.B.4. Planned Data Collection and Future Data Sharing**

- Medical Record Requests. Requests will be made of participants with certain procedures/conditions for an additional consent for medical/dental records. Medical records contain specific information that might be hard for women to recall, and medical record review allows validation of exposures reported by the mother in the CATI. Initial topics for which medical records will be requested include fertility treatments and dental treatments (See Attachments 19-22). The medical record review section of BD-STEPS depends on availability of funds and will not initiate at study onset.
- On Line Modules. With increasing access to and use of the internet, online questionnaires are an increasingly functional platform for obtaining data. As a pilot project within BD-STEPS, specific online questionnaire modules will be developed that are administered to only a select group of BD-STEPS participants identified through information reported in the CATI. For these pilots the likely initial topics will include occupational exposures among nurses (because of the high likelihood of internet access among this group and the specific, potentially teratogenic exposures that depend on the

details of the job, such as exposure to anesthetic gases) and confirmation of specific medication exposures (because of the opportunity to show pictures of pills, pill bottles and boxes).

- Global Unique Identifier. In the future, it is possible that a Global Unique Identifier (GUID)(9) among different birth defects researchers will be created. In a field with outcomes as rare as birth defects, the GUID will be helpful to link between different studies.
- Other Contact. Other potential future contact includes contact of some mothers for additional information (e.g. access to care) or long term outcomes (e.g. co-morbidities).

#### **4.C. Thank You Letter**

Immediately following completion of the interview, subjects are sent the interview thank you letter, which is mailed by the local site (Attachment 23). For some centers, the thank you letter will also serve as a request for residual newborn screening bloodspots and will be accompanied by a written consent form and a \$10 gift card.

#### **4.D. Newsletter**

With the thank you letter we will send a link to the current NBDPS newsletter, which contains information about BD-STEPS and the progress and findings of NBDPS to date (Attachment 24). Through the newsletter and other features on the BD-STEPS web site, we intend to inform study participants of general study progress and research findings, as analyses are completed. BD-STEPS newsletters that describe the status and completed work of studies using BD-STEPS data will be made available to past participants on approximately a yearly basis on the NBDPS and BD-STEPS websites.

## 5. BIOSPECIMEN COLLECTION, PROCESSING, AND STORAGE

### 5.A. Biologic Specimens

In an effort to improve our understanding of the etiology of birth defects, particularly in the area of gene-environment interactions, we hope to collect saliva from all participants, and in some states newborn screening bloodspot samples for use in the evaluation of biologic markers of exposure and susceptibility. Individual susceptibility (biomarkers of susceptibility) to the effects of environmental agents may vary depending on specific genetic or other factors (e.g., nutrition or immune function). If the effect of an exposure on the occurrence of birth defects depends on the interaction between the exposure and genetic susceptibility, then neglecting to study such interaction may lead to inaccurate estimates of the magnitude of the association between the exposure and the outcome.

Newborn screening is completed by collecting blood from infant heel sticks on filter paper soon after the infant's birth. Some state health departments store these bloodspot samples in a manner that would allow retrieval if parental consent was obtained. Some CBDRP can get access to the retained dried bloodspots which allows for the possibility of bloodspots to be linked to BD-STEPS data.

For the states that require consent for access of newborn bloodspots, a request for sharing of residual newborn bloodspots is included in the interview thank you letter (Attachment 23) along with a \$10 gift card, and a written consent form pertaining to bloodspots (Attachment 25).

If the consent form for residual newborn bloodspots is sent and not returned within two weeks, Central Interviewer staff will call the mother to see if she has any questions about the consent for newborn bloodspots (Attachment 37). The interviewer may obtain verbal consent (if allowed by the local Center's IRB) at this time if parents cannot read the written consent form or if they prefer verbal consent. If there is no response after one round of reminder calls, the family's participation status will be updated in the Clinical database. Newborn bloodspot materials are included as Attachments 23, 25-27, and 37).

When funds become available for saliva collection, saliva collection kits will be mailed to each mother who completed the interview and will include collection devices for her child (if living), herself, and the child's father. The collection kits will include a letter describing saliva collection (Attachment 28), an informed consent to request the residual newborn bloodspots (in states that allow retrieval of residual bloodspots)(Attachment 25), simple instructions, a gift card, material for completing the specimen collection, a Frequently Asked Questions form, and prepaid U.S. mail packets for specimen return.

After two weeks, if the completed saliva collection kit is not returned, Central Interviewer staff will place reminder calls to the mother to see if she has any questions about how to complete the kit followed by a reminder letter sent by the local site. If there is still no response after two rounds of reminder calls and letters, a final letter is sent to the mother encouraging her to complete the kit and stating that if the kit is not received within 2 weeks, we will assume she is not interested in participating. Saliva collection materials are included as Attachments 29-34.

**5.A.1. Written Consents**

At the study onset, select states will use a specific written consent for retrieval of residual newborn bloodspots; when saliva collection begins, there will be specific saliva consent forms as well as consent forms that will cover both bloodspots and saliva samples. The BD-STEPS draft consent for bloodspots is included as Attachment 25. The current bloodspot consent and the future saliva/bloodspot consent will include the following information: the purpose of the study, the procedures for analysis of the genetics and biomarker data (including the potential use of genetics and health information data for future data linkage projects), risks and benefits, information on confidentiality (including the study's Certificate of Confidentiality), compensation, research laboratories, the participant's right to refuse or withdraw samples, control, ownership, commercial value of biologic materials, and phone numbers for questions about the research or the participant's rights as a human subject.

All written consent documents for the collection of biologics inform participants that the CBDRP scientists intend to conduct genetic research that is directly related to birth defects in the BD-STEPS Central Laboratory and/or other CBDRP laboratories. The written consent form explicitly states:

“These samples will be used to study genes, which may play a role in why some babies have birth defects. They will only be used to study birth defects and for no other purpose.”

If parents cannot read the written consent forms or if they prefer verbal consent, they are read a verbal consent form by an interviewer. If a mother does not return the signed consent form allowing us to request some or all of her child's residual newborn bloodspots, for states where

consent is required, the bloodspots will not be requested. If mothers return saliva samples without the signed informed consent form, they are called and given the opportunity for verbal consent or, if they prefer to have another consent form sent to them, it is mailed to them along with a postage-paid return envelope. If mothers are not reachable by phone, a second consent form is mailed to them. If a mother does not return the signed consent form(s) but has returned the saliva samples, her family's saliva samples will be included in the study. By returning the saliva samples, these mothers have implied their consent to participate. Some study sites might be required to obtain written informed consent from each participant for saliva samples. If that is the case, specimens received without a written informed consent will be excluded.

The BD-STEPS biologic consent for residual newborn bloodspots and, in the future, for saliva will contain a new section, "Sharing your genetic and health information for future research," which was not in the previous NBDPS written (genetics) consent. This section was added because of a National Institutes of Health (NIH) Genome-Wide Association Study (GWAS) policy that requires data from NIH-supported GWAS be deposited into the NIH GWAS data repository, currently designated as the **database of Genotypes and Phenotypes (dbGaP)**. See p. 3 of the consent (Attachment 25) for additional language that describes how these data potentially will be shared.

The consent form (Attachment 25) also states the following:

"For any tests that have clinical importance, we will publish summarized results in the study newsletter. This newsletter is available to all participants when it is published on line each year at [www.bdsteps.org](http://www.bdsteps.org)."

If we receive a request for the results of individual genetic tests carried out in BD-STEPS, we will comply with the Privacy Act and respond in the following way:

We will reiterate what was included in their written consent, which stated that results from these studies are not meant to test individual medical status and were completed in research labs so we do not plan to return any individual results. We will explain the limitations of the testing that was done (e.g. testing was completed in non-CLIA certified labs) and explain that tests of clinical importance will be published as summarized results in the study newsletter. We will also suggest that participants discuss any genetic tests that they think would be useful to them with their health care provider, and will offer to assist them in locating a provider.

We have developed a fact sheet for newborn bloodspots that can be sent to anyone requesting information on the genetic testing done as part of BD-STEPS (Attachment 27). The fact sheet explains the nature of the testing that is completed on the biologic samples, the limitations of the technology being used, why individual test results will not be reported, how a participant can withdraw from the study and other relevant information.

CDC IRB approval (protocol 2087) of an amendment for a “Waiver of Consent for infant participants when they reach the age of 18” was obtained on January 31, 2013. Infant participants will not be re-contacted. According to 45 CFR 46.116, “an IRB may ...waive the requirements to obtain informed consent provided the IRB finds and documents that: 1)The research involves no more than minimal risk to the subjects; 2)The waiver or alteration will not adversely affect the rights and welfare of the subjects; 3)The research could not practicably be carried out without the waiver or alteration; and 4)Whenever appropriate, the subjects will be provided with additional pertinent information after participation.”

**5.A.2. Incentive**

For BD-STEPS sites obtaining newborn bloodspot consents, requests for parents to consent to retrieval of some or all of their infant's residual bloodspots will include a \$10 gift card. Each of the BD-STEPS sites will also include a gift card with the saliva collection kit when this portion of the study starts.

**5.B. Receipt of Biologic Material**

The residual newborn bloodspots will either be retained at a state laboratory storage facility, with the local Center only retaining the consent, or the local Center will physically get some or all of the bloodspots from the State and store them locally. When saliva collection begins, the saliva kits will be sent directly from each participant to local Centers. Local Center staff will mark consent forms (saliva and dried bloodspots) as received in BD-STEPS workflow system and change the participation values in the clinical database and will be responsible for storing them in a secure manner. For saliva collection, local Center staff will scan barcodes on labels affixed to the saliva collection devices into the biologics software. Biologic samples obtained as part of BD-STEPS are stored in a secure manner without identifiers (with the exception of study identification number) in secure storage facilities.

**5.C. Final Thank You and Incentive**

A thank you letter (Attachment 26) without a gift card is sent upon receipt of the consent form to retrieve newborn bloodspots. If, in the future, saliva collection kits are received back, each of the BD-STEPS sites will send a final letter of thanks and an additional gift card to each participating mother (Attachment 30).

**5.D. Central Laboratory and Quality Control**

When the saliva collection portion of the study becomes active, a Central Laboratory will be employed to process saliva samples and complete quality control analyses. Quality control data for each sample will be stored in a laboratory information management system. Access to the system will be limited to the BD-STEPS and Central Laboratory staff who are responsible for the data. These data will be stored using a nine-digit study identification number and will be maintained using stringent security measures. Bloodspots will be retained locally either by the Center or at the state departments of health. Each Center will be responsible for processing and completing quality control analyses on the bloodspot samples before the samples are used.

**5.E. Central Biorepository**

Use of biospecimen storage banks is becoming increasingly important for epidemiologic research for several reasons. Major expenditures in time and money are spent in sample collection. Maintaining biospecimen banks, which provide the opportunity for additional research as new hypotheses or improved technologies emerge, allows the potential contributions of study participants to be maximized. This approach is particularly important for testing hypotheses regarding risk factors for birth defects. Because individual defects are rare, many years of data collection are required to obtain enough samples to complete a valid etiologic study for a specific birth defect. The length of time between obtaining the specimen and having adequate numbers for a specific analysis is likely to be a minimum of three to five years, and may well be much longer. Participants will be informed of the intent to bank their specimens for birth defects research.

When the saliva collection portion of the study becomes active, after saliva collection kits are returned and consent forms are removed and stored securely, the saliva specimens will be sent to a centralized storage facility. The samples will be stored in a manner that permits efficient retrieval and optimum stability; they can be identified only by the study identification number. The biorepository will release specimens only on the authorization of the CDC Collection Custodian (Mary Jenkins, PhD).

It is the expectation of scientists within the CBDRP that a portion of the DNA will be banked for very long-term research studies, perhaps even decades in the future, when the technologies available are likely to be able to make use of these samples in ways that can only be imagined now. These samples will be stored indefinitely unless a request is received from the participant to destroy them.

Of note: There is no commercial value in these samples and profits from any materials associated with this study are not expected. The samples will not be used for commercial purposes and neither researchers nor study participants will receive profits from the donated materials.

## **6. BD-STEPS Data Analysis**

### **6.A. Data Sharing**

The Data Sharing Committee has voting representatives from each CBDRP. The NBDPS Data Sharing Committee established guidelines for access to the compiled interview and biologic data and is responsible for ensuring that the data are shared equitably; these same guidelines will be used for BD-STEPS (Attachment 35). Any of the CBDRP researchers interested in using the pooled data for analysis submits a letter of intent and later a more detailed proposal to the

committee for review. The committee considers the scientific merit of the proposals and encourages collaboration among the researchers where possible. The committee will use guidelines established in NBDPS for authorship, acknowledgments, and other issues related to the publication of studies using the collective data (Attachment 35); the committee will also ensure that all proposed research complies with human subjects' requirements. Additional IRB review will be required for any studies that fall outside of the scope of the current protocol.

## **6.B. Data Preparation**

The interview data from the local CDRP will be combined into databases by the CDC programmers for use in statistical analyses by analysts at each of the CDRP. Data will be released 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.

### **6.B.1. Clinical Data Classification**

Numerous studies have documented extensive etiologic heterogeneity in birth defect cases with similar anatomic appearance and/or proximity. To provide a sound epidemiologic framework to study specific defects, the presence of associated defects, and accurate clinical descriptions of defect types should be used in classifying birth defect cases into subgroups that are etiologically and pathogenetically homogeneous. All BD-STEPS cases are classified by clinical geneticists, or, where appropriate, pediatric cardiologists. Each case is classified as to whether it occurs in isolation or in addition to other defects. Heart defects are additionally classified as to whether the heart defect is simple or complex, indicating whether there was a single heart defect or multiple heart defects.

### **6.B.2. Interview Data Coding**

The interview instrument will contain open-ended questions that will be coded by the CDC-contracted interviewing facility into variables that will be easier to analyze. Examples of such open ended questions include occupational information and family history of birth defects.

### **6.B.3. Geocoding of Address Data**

During the interview portion of the study, information is collected on residential addresses at the estimated time of conception. Geocoding this information (i.e. assigning geographic coordinates) will be extremely valuable for studies of environmental health as well as other topics through linking of spatially-coded exposure data. For example, geocoding will allow studies to assess whether proximity to certain types of locations, such as factories, toxic waste dumps, nuclear power plants, or health care facilities are associated with risk of the studied defects. It will also allow participants to be assigned, based on their residences, to their drinking water source, geological regions (e.g. high radon areas), areas of water treatment utilities, plumes from pollution sources, and census tracts, for which a variety of associated socioeconomic variables are available.

The CDRPs will conduct centralized geocoding for all interviewed cases and controls, which will maximize consistency in geocoding across Centers. The residential data will not be centrally available, and some states will require that all the geocoded and original address data be returned to them. After the centralized geocoding is complete, all geocoded data will be returned to the Center of origin; a centralized repository of the geocodes will NOT be maintained at CDC.

The Geospatial Research, Analysis, and Services Program of ATSDR have offered in the past to geocode all NBDPS residence data from all Centers, at no cost, and they will be approached again. This group, external to BD-STEPS, does not need any information about BD-STEPS participants besides the actual address. They will only know that a woman lived at that address at the beginning of her pregnancy and participated in BD-STEPS interview.

### **6.C. Data Analysis Databases (Tools)**

The combined data from all BD-STEPS sites will be released after the classification and coding have been completed. Data will be released in a standardized data format to all the participating BD-STEPS sites. Analysts are required to complete training on the use of the data analysis tools and to have received approval from the Data Sharing Committee of their analytical proposal prior to beginning data analysis.

### **6.D. Biologics**

#### **6.D.1. External Quality Assessment**

To ensure that each lab actively involved in genetic and epigenetic analyses of BD-STEPS specimens is proficient in their respective laboratory techniques independent of the source material or extraction procedure, an external quality assessment (EQA) that was developed for the NBDPS will be amended and will be used for laboratories planning to conduct research using BD-STEPS saliva samples (when saliva collection begins). The same EQA protocols that were approved by the NBDPS Coordinating Council will be used for BD-STEPS and are included as Attachments 36A, 36B, and 36C.

### **6.D.2. Biorepository Sample Requests**

When the saliva collection portion of the study becomes active, saliva specimens stored in the BD-STEPS biorepository will be used to evaluate genetic susceptibilities to birth defects using candidate genes, genome wide associations, copy number variants, epigenetics, sequencing, and other emerging technologies. The CBDRP scientists will share aliquots of these samples, without personal identifiers, to carry out collaborative research studies, following the approval of proposed research projects by the Data Sharing Committee (Attachment 35). As previously mentioned, sharing of samples with collaborating investigators is done without personal identifiers, and only the CDC Collection Custodian can make a biorepository sample request. The CBDRP investigators submit sample requests to the CDC, and CDC CBDRP staff process requests to ensure that each of the CBDRP receives their allotted portion of samples. Only researchers within the CBDRPs will be allowed to request these biospecimens. Investigators retain control of biological materials obtained at their CBDRP, unless the participant requests that these materials be destroyed.

### **6.D.3. Genetic Analyses Database**

The NBDPS has established a centralized database to store results from genetic analyses that will also be used to store genetic results from BD-STEPS. Centralized storage of genetic data from saliva (once this portion of the study begins) will facilitate data sharing between CBDRPs. Centralized storage of genetic data from bloodspots is not required but is strongly encouraged to enhance the data repository. Genetic data that have coded identifiers are submitted to CDC via SAMS. These data are compiled and maintained by the CDC in a commercial off-the-shelf

database that has been certified through CDC's Certification and Accreditation process. The combined data from all completed analyses will be released annually to BD-STEPS analysts.

**6.E. Publications**

BD-STEPS study sites are expected to write several publications per year analyzing NBDPS or BD-STEPS data or combining the NBDPS and BD-STEPS data. In the author list "Birth Defects Study To Evaluate Pregnancy exposureS" will be included as an author if pooled data are included and the CDC funding will be acknowledged in the funding section.

## References

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**Complete list of BD-STEPS Attachments**

BDSTEPS-Att1	Birth Defects Prevention Act of 1998
BDSTEPS-Att2	Certificate of Confidentiality
BDSTEPS-Att3	State BD Surveillance Programs 9-07
BDSTEPS-Att4	Letter of Authorization DCH2012-13
BDSTEPS-Att5	BD Studied
BDSTEPS-Att6	Intro Letter*
BDSTEPS-Att7	Human Subjects Fact Sheet*
BDSTEPS-Att8	Calendar*
BDSTEPS-Att9	QA Intro Sheet*
BDSTEPS-Att10	Medication Summary*
BDSTEPS-Att11	Address Correction Form*
BDSTEPS-Att12	No Phone Letter*
BDSTEPS-Att13	Voicemail Scripts*
BDSTEPS-Att14	Cell Phone Texts and Email Scripts*
BDSTEPS-Att15	Final Letter*
BDSTEPS-Att16	Soft Refusal Letter*
BDSTEPS-ATT17	Intro Phone Scripts*
BDSTEPS-Att18	CATI Questionnaire*
BDSTEPS-Att19	Letter for Participant for Medical Records*
BDSTEPS-Att20	Letter for Health Care Professional for Medical Records*
BDSTEPS-Att21	Follow up Phone Script*
BD-STEPS-Att22	Medical Records Release Form*
BDSTEPS-Att23	Thank you Letter and Optional Bloodspot Intro*
BDSTEPS-Att24	NBDPS Newsletter*
BD-STEPS-Att25	Bloodspot Consent *
BD-STEPS-Att26	Bloodspot Thank You Letter*
BD-STEPS-Att27	Bloodspot FAQ*
BDSTEPS-Att28	Saliva Collection Intro Letter*
BDSTEPS-Att29	FAQ Saliva Collection*
BDSTEPS-Att30	Saliva Collection Thank You Letter*
BDSTEPS-Att31	Saliva Collection Scripts*
BDSTEPS-Att32	Saliva Collection Instructions/Parent*
BDSTEPS-Att33	Saliva Collections Instructions/Child*
BDSTEPS-Att34	Saliva Reminder Letter*
BDSTEPS-Att35	DS Guidelines
BDSTEPS-Att36A	EQA Genotyping
BDSTEPS-Att36B	EQA Methylation
BD-STEPS-Att36C	EQA Sequencing
BD-STEPS-Att37	Bloodspot Reminder Script*

\*=Submitted for Spanish translation

