



Centers for Disease Control

National Center on Birth Defects and Developmental Disabilities Extramural Research Program
Office

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

RFA-DD-18-001

Application Due Date: 02/22/2018

Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS) II
RFA-DD-18-001
TABLE OF CONTENTS

[Part 1. Overview Information](#)

Key Dates
Required Application Instructions
Executive Summary

[Part 2. Full Text](#)

[Section I. Funding Opportunity Description](#)

[Section II. Award Information](#)

[Section III. Eligibility Information](#)

[Section IV. Application and Submission Information](#)

[Section V. Application Review Information](#)

[Section VI. Award Administration Information](#)

[Section VII. Agency Contacts](#)

[Section VIII. Other Information](#)

Part 1. Overview Information

Participating Organization(s)

Centers for Disease Control

Components of Participating Organizations

National Center on Birth Defects and Developmental Disabilities Extramural Research Program Office (NCBDDD ERPO)

National Center on Birth Defects and Developmental Disabilities (NCBDDD)

Notice of Funding Opportunity (NOFO) Title

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

Activity Code

U01

Notice of Funding Opportunity Type

New

Agency Notice of Funding Opportunity Number

RFA-DD-18-001

Catalog of Federal Domestic Assistance (CFDA) Number(s)

93.073

Category of Funding Activity:

Health

NOFO Purpose

AMENDMENT #1: To add clarification language per the Questions and Answers listed in Appendix A: Potential Applicant Questions and CDC Response. Changes in red font.

The purpose of this NOFO is to identify causes of certain major, structural birth defects and stillbirths using epidemiologic and genetic research methods and to provide information that could be translated into public health prevention messages.

Component A. BD-STEPS II Core. To support the epidemiological and genetic research capabilities of the Centers for Birth Defects Research and Prevention (CBDRP) through the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS). BD-STEPS is a case-control study of genetic and environmental risk factors for birth defects that focuses on the key areas of: (1) maternal chronic diseases and their treatments; (2) infectious disease in pregnancy; and (3) medications.

Component B. BD-STEPS stillbirth. To support the exploration of modifiable risk factors for stillbirths. Component B applicants must also apply for Component A.

Key Dates

Publication Date:

To receive notification of any changes to RFA-DD-18-001, return to the synopsis page of this announcement at www.grants.gov and click on the "Send Me Change Notification Emails" link. An email address is

Letter of Intent Due Date: needed for this service.
[Insert 30 days from date of publication]

Application Due Date: 02/22/2018

On-time submission requires that electronic applications be error-free and made available to CDC for processing from eRA Commons on or before the deadline date. Applications must be submitted to and validated successfully by Grants.gov/eRA Commons no later than 5:00 PM U.S. Eastern Time. Note: HHS/CDC grant submission procedures do not provide a period of time beyond the application due date to correct any error or warning notices of noncompliance with application instructions that are identified by Grants.gov or eRA systems (i.e., error correction window).

Scientific Merit Review: 04/05/2018

Secondary Review: 05/03/2018

Estimated Start Date: 09/01/2018

Expiration Date: 02/21/2018

Due Dates for E.O. 12372: Executive Order 12372 does not apply to this program.

Required Application Instructions

It is critical that applicants follow the instructions in the [SF 424 \(R&R\) Application Guide](#) except where instructed to do otherwise in this NOFO. Conformance to all requirements (both in the Application Guide and the NOFO) is required and strictly enforced. Applicants must read and follow all application instructions in the Application Guide as well as any program-specific instructions noted in Section IV. When the program-specific instructions deviate from those in the Application Guide, follow the program-specific instructions.

Note: The Research Strategy component of the Research Plan is limited to 25 pages.

Applications that do not comply with these instructions may be delayed or not accepted for review.

Telecommunications for the Hearing Impaired: TTY 1-888-232-6348

Executive Summary

Purpose. CDC has previously implemented population based case control studies of birth defects known as the National Birth Defects Prevention Study (NBDPS) for births from 1997-2011 and the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS I) which started with births in 2014 and is ongoing. The purpose of BD-STEPS II is to identify causes of birth defects and stillbirths using epidemiologic and genetic research methods and provide information that could be translated into public health prevention messages.

The activities under this NOFO will be supported by two separate but related funding

components:

1. Component A. BD-STEPS II Core. To support the epidemiological and genetic research capability of the Centers for Birth Defects Research and Prevention (CBDRP) through BD-STEPS. The intent of BD-STEPS II is to carry out the same basic BD-STEPS study design with a focus on the key areas of: (1) maternal chronic diseases and their treatments; (2) infectious disease in pregnancy; and (3) medications. In BD-STEPS II, we will add the focus area of infectious causes of birth defects, and pilots will be conducted to determine feasibility of medication use validation. Both new sites and current BD-STEPS sites are encouraged to apply for this component. Maintaining the same basic study design and overall protocol integrity will allow for data pooling across NBDPS, BD-STEPS I, and BD-STEPS II.
2. Component B. BD-STEPS stillbirth. To support the exploration of modifiable risk factors for stillbirths. The intent of this component is to conduct a case-control study of stillbirth risk factors using the BD-STEPS II Core interview and a follow-up interview with mothers affected by stillbirths and mothers of livebirths. To be funded for Component B, applicants must have a responsive application for Component A and receive Component A funding. Both new sites and current BD-STEPS sites are encouraged to apply for this component.

Applicants should clearly indicate the Component(s) for which they are applying and should include at the beginning of the title, the Component(s) under which the application should be considered (i.e., Component A or Component B). Separate applications are required for each Component.

- **Mechanism of Support.** Cooperative Agreement
- **Funds Available and Anticipated Number of Awards.** We anticipate 5 – 7 awards being made for Component A under this NOFO, with 2 recipients also receiving funding for Component B. The estimated total level of funding for Components A and B (direct and indirect for entire project period) is \$28,500,000. Awards issued under this NOFO are contingent upon availability of funds and a sufficient number of meritorious applications. Because the nature and scope of the proposed research will vary from application to application, it is also anticipated that the size and duration of each award may also vary. The total amount awarded and the number of awards will depend upon the number, quality, duration and cost of the applications received.

- **Budget and Project Period.**

1. **Component A. BD-STEPS II Core:** The estimated total funding (direct and indirect) for the first budget period, 9/1/2018-8/31/2019, is \$5,300,000. The estimated total funding (direct and indirect) for the entire project period, 9/1/2018-8/31/2023, is \$26,500,000. Estimated Number of Awards: up to 7. Average annual amount of each award is \$800,000-\$900,000.
2. **Component B. BD-STEPS Stillbirth:** The estimated total funding (direct and indirect) for the first budget period, 9/1/2018-8/31/2019, is \$400,000. The estimated total funding (direct and indirect) for the entire project period, 9/1/2018-8/31/2023, is \$2,000,000. Estimated Number of Awards: up to 2.

Average annual amount of each award is \$200,000.

- **Application Research Strategy Length:** Page limits for the Research Strategy are clearly specified in [Section IV. Application and Submission Information](#) of this announcement.
- **Eligible Institutions/Organizations.** Institutions/organizations listed in [Section III, 1.A.](#) are eligible to apply.
- **Eligible Project Directors/Principal Investigators (PDs/PIs).** Individuals with the skills, knowledge, and resources necessary to carry out the proposed research are invited to work with their institution/organization to develop an application for support. NOTE: CDC does not make awards to individuals directly. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply.
- **Number of PDs/PIs.** Applications may include more than one PI; however, the first PI listed on the application will be the “contact PI” for all correspondence. Any additional PIs are permitted, but would be referred to as Co-PIs.
- **Number of Applications.** Eligible applicant institutions may submit more than one application for each component, provided that each application is scientifically distinct.
- **Application Type.** New
- **Special Date(s).** Not Applicable.
- **Application Materials.** See [Section IV.1](#) for application materials. Please note that Form D is to be used when downloading the application package. <http://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/general-forms-d.pdf%20>
 - **Hearing Impaired.** Telecommunications for the hearing impaired are available at: TTY: 1-888-232-6348.

Part 2. Full Text

Section I. Funding Opportunity Description

Statutory Authority

This program is authorized under Sections 301 and 317C of the Public Health Service Act [42 U.S.C. 241, and 247b-4 as amended].

1. Background and Purpose

The National Center on Birth Defects and Developmental Disabilities (NCBDDD), Division of Congenital and Developmental Disorders (DCDD), seeks to fund a collaborative project for a multi-site case control study of selected major birth defects and stillbirths.

Birth defects affect about three percent of all births in the United States and are a leading cause of infant mortality, morbidity, and healthcare costs. Birth defects account for one in five infant deaths and contribute substantially to long-term disability. Although several human teratogens and genetic factors have been identified, the causes of two-thirds of birth defects remain unknown. It is important to study specific birth defects individually, because the etiology of specific birth defects may differ substantially. Because individual types of birth defects are relatively rare, it has been difficult in the past to conduct a study large enough to provide the

necessary power to assess risk factors for specific defects(1).

Overview of Funding History

In 1996, Congress appropriated funds to initiate some of the activities described in the Birth Defects Prevention Act of 1998, including the funding of the Centers for Birth Defects Research and Prevention (CBDRP). Since FY 1996, cooperative agreements have been awarded to 9 different states(2). The two major collaborative activities of this project have been multi-site case-control studies called the National Birth Defects Prevention Study (NBDPS) and the Birth Defects Study to Evaluate Pregnancy exposureS (BD-STEPS). Both rely on data from the existing birth defects surveillance systems.

CBDRP Study Designs (NBDPS and BD-STEPS)

Data collection for the NBDPS began for births on or after October 1, 1997 and ended with births on December 31, 2011, the last interview was conducted in March 2013(3, 4). Up to 9 sites were funded during the study period and CDC was included as an additional study site. Pregnancies affected by one of more than 30 major structural birth defects and those unaffected by a major structural birth defect were ascertained using birth hospital medical records and vital records, respectively. Clinicians used standard definitions to review cases for eligibility(5, 6). If the birth defect was known or strongly suspected to be caused by a syndrome or other known genetic or teratogenic factor, the case was excluded. Computer-assisted telephone interviews were conducted with more than 40,000 women, who were asked about exposures from 1 month before through the end of pregnancy. At the end of the maternal interview, mothers were sent buccal (cheek) cell collection kits to collect cells from themselves, the biological father, and the infant (if living)(7).

In September 2013, NCBDDD funded 6 study sites (with CDC serving as the 7th site) to conduct BD-STEPS I, which extended and focused the data collection efforts of the NBDPS. A subset of 17 NBDPS birth defects were included, those which are most reliably ascertained and likely to have the greatest public health importance. In this NOFO, we will refer to the currently funded BD-STEPS as BD-STEPS I and the plans for BD-STEPS as described in this NOFO will be referred to as BD-STEPS II. In BD-STEPS I, the maternal interview was modified to limit the exposure period to the month before and the first 3 months of pregnancy and to better capture certain exposures; however, many of the questions from the NBDPS interview are included in the BD-STEPS I interview, and due to the similarity in study methods, data will be able to be combined across studies. BD-STEPS I incorporates online questionnaires to obtain more detailed information about exposures women report during the phone interview. The first online questionnaire focuses on occupational exposures. In order to be able to assess genetic risk factors for birth defects, access to residual newborn bloodspots to use in genetic research is being requested from mothers in most BD-STEPS sites.

In addition, two of the BD-STEPS I study sites include stillbirths without birth defects as a separate case group to allow research of this understudied birth outcome. Women with pregnancies affected by a stillbirth (pregnancy loss at 20 or more weeks of gestation) and women with pregnancies unaffected by a stillbirth or birth defect are asked to complete a follow-up interview after the BD-STEPS Core interview to collect information on exposures later in pregnancy and exposures most relevant to elucidating causes of stillbirths.

The CBDRP has been a collaborative effort between CDC's NCBDDD and the funded

recipients. For the past 20 years, the CDBRP case-control studies have provided a unique and unprecedented opportunity to assess a variety of exposures for their potential association with specific birth defects.

The research experience from the CDBRP collaboration demonstrated several areas in which public health birth defects research could benefit from further study. As an example, although the association between diabetes, obesity and specific birth defects was observed in the analyses from the collaborative projects, it is not clear whether changes in body fat distribution or increasing physical activity might mitigate some of the negative impact of obesity and diabetes on birth defects. Evaluating this relationship is an important next step if targeted and appropriate public health recommendations for maximum public health impact need to be made. For studies assessing medications, experience from this collaborative research demonstrates the importance of documenting the indication for which the medication was taken (e.g. fever vs. pain for acetaminophen) and the dose that was consumed (e.g. 25 to 200 mg/day for sertraline). These data were not available from the NBDPS but are available in BD-STEPS I.

This notice of funding opportunity will continue to support the infrastructure of CDBRP's Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS II). Component A will be an open competition to identify study sites with the capability to conduct the epidemiological and genetic research of BD-STEPS I with a focus on the key areas of (1) maternal chronic diseases and their treatments; (2) infectious disease in pregnancy; and (3) medications. By including multiple study sites, BD-STEPS II will aim for a study population that is representative of the US population with regards to the racial/ethnic composition of the study regions. Implementing BD-STEPS II will increase the total pooled sample size especially for some rarer exposures and less common birth defects. The addition of some birth defects and the ascertainment of infection status from the state health department will allow a new focus on infectious causes of birth defects and, with the focus on medications, BD-STEPS II will provide the opportunity to look at newly released medications and provide current prevalence of prescription and over-the-counter medication use during pregnancy.

Component B provides an opportunity for up to 2 successful Component A applicants to explore modifiable risk factors for stillbirths.

Healthy People 2020 and other National Strategic Priorities

This program addresses the "Healthy People 2020" objective to reduce the rate of infant mortality related to birth defects and due to congenital heart defects (MICH-1.6 and MICH-1.7) and the objective to reduce the prevalence of spina bifida (MICH-28.2).

Measurable outcomes of the program will be in alignment with the first performance goal for the National Center on Birth Defects and Developmental Disabilities: Prevent major birth defects attributable to maternal risk factors.

Public Health Impact

Birth defects account for one in five infant deaths and contribute substantially to childhood morbidity and long-term disability. Currently, the causes of two-thirds of birth defects are unknown. This NOFO supports the continuation of BD-STEPS I data collection, which will increase the sample sizes of individual birth defects for investigation of high priority hypotheses, thereby enhancing the potential of BD-STEPS to successfully investigate birth

defect risk factors. BD-STEPS II will also allow for the ascertainment of newly released medications, as new drugs get released every year. This is especially important since pregnant women are usually not included in clinical trials. The recent Zika outbreak has highlighted the devastating effect external factors can have on the developing fetus. In BD-STEPS II, we will explore the feasibility of looking at maternal infectious diseases as a cause of birth defects.

Each year, more than 26,000 pregnancies in the U.S. end in a stillbirth (pregnancy loss at 20 or more weeks of gestation). Stillbirths are an under-evaluated and under-reported public health issue. There is little information on the causes of stillbirths. This NOFO supports investigations of risk factors for stillbirths by asking women affected by stillbirths and those unaffected by stillbirths to complete a follow-up interview after the BD-STEPS Core interview that includes questions designed to elucidate risk factors of stillbirth. This represents a unique opportunity in a currently underexplored area.

Relevant Work

The CDBRP has been a collaborative effort between CDC's NCBDDD and the funded recipients. For the past 20 years, the CDBRP case-control studies have provided a unique and unprecedented opportunity to assess a variety of exposures for their potential association with specific birth defects. Over 250 publications in peer-reviewed journals have reported data from the collaboration, and results from analyses have also been disseminated through conference proceedings and coverage by the popular press. A few highlights of these findings are described here: (1) The relationships between obesity and diabetes and specific birth defects have been elucidated by using data from the collaborative projects; (2) Results from the analysis assessing selective serotonin reuptake inhibitors (SSRIs) and specific birth defects contributed important information for decision-making when treating pregnant women with depression; (3) Data from the collaborative projects have also been used to confirm previous observations of an association between the use of opioid analgesics and spina bifida and heart defects, as well as the association between maternal smoking and orofacial clefts; and (4) Gastroschisis, a defect with increasing prevalence that is strongly associated with young maternal age, was found to be associated with report of genito-urinary infections early in pregnancy.

2. Approach

To meet the goals of the NOFO, this opportunity includes 2 separate funding components:

1. Component A. BD-STEPS II Core will support the epidemiological and genetic research capability of the Centers for Birth Defects Research and Prevention (CDBRP) through the Birth Defects Study To Evaluate Pregnancy exposures (BD-STEPS I). This new opportunity will allow for increased sample size for some of the rarer exposures, and will add a new focus on infectious causes of birth defects.
2. Component B. BD-STEPS stillbirth will support the exploration of modifiable risk factors for stillbirths. To be funded for Component B, applicants must have a responsive application for Component A and receive Component A funding.

Applicants should clearly indicate the Component(s) for which they are applying and should include at the beginning of the title, the Component(s) under which the application should be considered (i.e., Component A or Component B). Separate applications are required for each

Component.

Objectives/Outcomes

Component A: BD-STEPS II Core

a. To collect information on early pregnancy exposure to modifiable risk factors via a maternal telephone interview with a specific focus on:

1. ***Maternal chronic diseases and their treatments:*** Certain chronic conditions are increasingly common among women of childbearing age, and therefore also among pregnant women. In BD-STEPS I, we introduced innovative questions to the maternal interview on asthma, autoimmune disease, diabetes, obesity and thyroid disease. As the medical field is advancing, women survive severe illness and become pregnant after surviving cancer or transplants. BD-STEPS explores these exposures and the medications that women take for these conditions. Regarding obesity, it is not clear whether body fat distribution or increasing physical activity might impact the association of obesity and birth defects. The BD-STEPS interview allows collection of information on these factors, and builds on the existing data from the NBDPS to provide more power than any previous study to assess the interrelation of these factors, an important next step if we want to develop effective public health interventions. Mental health conditions including depression, anxiety, stress, and insomnia have the potential to impact pregnancy through manifestations of the condition, the exposures potentially increased as a consequence of the condition (e.g. smoking or alcohol use), and medications taken to control the condition. The BD-STEPS maternal interview captures this information and will allow better characterization of the birth defects risk associated with these conditions and any modifying factors that might reduce the risk.

2. ***Infectious disease in pregnancy:*** The outbreak of Zika virus has shown that novel causes of birth defects can be identified at any time. During the emergency response it became clear that this mosquito-borne and sexually transmitted flavivirus is associated with devastating birth defects when infection occurs during pregnancy. To allow for further investigation of infectious causes of birth defects new questions about possible exposure to infectious disease will be added to the questionnaire in BD-STEPS II and additional defects suspected to be associated with prenatal infectious disease will be added (i.e. microcephaly, eye defects, and arthrogryposis). It is expected that grantees working on BD-STEPS II will ascertain reportable disease records for consenting participants in their state health departments to ascertain diseases such as Zika, sexually transmitted diseases, and Lyme disease.

3. ***Medications:*** Approximately 50% of pregnant women take at least one prescription medication during the first trimester, and even more report the use of over-the-counter medications. Medications have the potential to act as strong teratogens, as evidenced by thalidomide and isotretinoin. New medication products are constantly being introduced to the market, but the randomized-controlled trials that test drug safety and efficacy typically exclude pregnant women. In addition, some medications are used for an expanded list of indications over time which can increase the likelihood of exposure, such as the use of some antiepileptic medications for migraines, a much more common condition in reproductive aged women. Increases in chronic disease among pregnant women translate to increases in long term exposure to maintenance medications to control their conditions, and data are needed to inform the public of the risk/benefit assessment of continuing to take a medication during pregnancy.

The BD-STEPS interview collects information on the condition for which the medication was taken (e.g. whether topiramate, an antiepileptic, is being used to control seizures, manage migraines, or assist with weight loss), and the dose that was consumed (e.g. for clomiphene citrate whether it was 50, 100, or 150 mg).

- b. To identify genetic or epigenetic risk factors or to validate environmental exposures through analysis of bloodspots. Mothers of all liveborn infants in BD-STEPS will be asked to consent for use of residual newborn bloodspots, if blood spots are retained in the state. The combination of genetic and interview data can allow for gene-environment interaction studies if the study population is large enough.
- c. To collaborate with all recipients and CDC to compile data repositories and to conduct epidemiological analyses to assess risk factors for birth defects.
- d. To train the future generation of birth defects researchers. Recipients will be expected to establish a training plan and employ junior researchers for training and mentoring such as Masters- and PhD-level students, post-doctoral fellows, medical students and residents, and other junior public health professionals. The training plan should address how junior researchers will gain skills in dysmorphology, birth defects epidemiology, and other study-related activities through this mentoring.
- e. To validate maternal self-reported medication use during pregnancy. Recipients will be required to conduct a pilot project that focuses on specific prescription medications, such as SSRIs, antihypertensives, or thyroid medications. Potential sources for validation data include, but are not limited to, electronic medical records, insurance records, or pharmacy records. The pilot project should encompass a full year of births and include an evaluation component. Results from the pilot studies will be used to inform validation projects to be implemented by all Centers across BD-STEPS.

Project management

Recipients are expected to develop a management and staffing implementation plan for the proposed program. This plan will include the provision of evidence of legal authority to access data needed to accomplish the activities required by this NOFO and the recipient's application, including HIPAA and IRB requirements. The recipient should also provide evidence of legal authority to share identifiable, individual-level contact information with CDC and its contractors and individual-level data without names and addresses with other recipients of this cooperative agreement to create a pooled analytic database. The updated Common Rule requires single IRB approval of cooperative (i.e., multi institutional) research conducted in the United States (<https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-01058.pdf>). The central IRB model is expected to be more efficient and require less personnel time and fewer resources than the previous model requiring review and approval from each institution's IRB. Compliance with this requirement starts January 20, 2020, which is within the timeframe of the current NOFO. The intent behind the delay is to provide time for development of institutional policies and procedures necessary for implementation. Thus, recipient's local IRBs will be expected to defer to the CDC IRB unless 1) the CDC determines and documents that use of a single IRB is not appropriate, or 2) the recipient is an institution that requires more than single IRB review by law (including tribal law). This policy does not relieve local study sites of their

obligations to protect human subjects.

For joint academic/state applications, the recipient will include documentation of a planned meaningful collaboration between the state health department and the academic center. If a center cannot defer to a central IRB, uniform study protocols and materials will need to be submitted to the local IRB without modification. If modifications are required by the local IRB, documentation needs to be provided to CDC, to consider implementation study wide.

Data and specimen collection

The recipients are expected to use data from existing, state-funded, population-based, birth defects surveillance systems to identify all cases (either live born, stillborn, or induced abortions) diagnosed with any of the proposed eligible birth defects (Table 1) in the first year of life. **If applicants do not currently track all of the birth defects listed in Table 1, they should describe as part of their application how they will incorporate case finding for these defects into their surveillance system.** Additional information needed to determine case eligibility or classification will be abstracted from hospital records or vital records by the recipient. The recipients will select a random sample of live births without major birth defects from the same source population as the cases to serve as the comparison group. These random samples are expected to include approximately 75-100 births for each study year at each study site. Recipients will describe the existing birth defects surveillance system, its attributes, its funding, and the geographical area the source population will encompass. Funds from this NOFO cannot be used to support the core birth defects surveillance system, but can be used to enhance the system (e.g., inclusion of prenatally diagnosed cases, improved timeliness). The recipient should be able to send 80% of the cases to the central interviewing contractor within 10 months after birth. The identified source population for the study should include between 30,000-75,000 births per year, and all cases identified in the source population with the defects listed in Table 1 should be considered eligible.

The recipients are expected to work with their State Health Department to obtain available information from the National Electronic Disease Surveillance (NEDS) System to ascertain any of the following tentative list of reportable conditions (Chickungunya, Chlamydia, Dengue fever, Gonorrhea, Hepatitis A B or C, Lyme disease, Malaria, Novel Influenza A virus, West Nile virus, Zika virus) that affected the participants in the two years before or during pregnancy. Participants will be asked for consent to link this information. The recipients will include requests to retrieve residual newborn bloodspots with the interview thank you letters, if they are able to retrieve and store bloodspots linked to the study participant.

Recipients are expected to conduct a pilot project to validate maternal self-reported medication use during pregnancy. These pilot projects should focus on specific prescription medications, such as SSRIs, antihypertensives, or thyroid medications. Potential sources for validation data include, but are not limited to, electronic medical records, insurance records, or pharmacy records. The pilot project should encompass a full year of births and include an evaluation component. Results from the pilot studies will be used to inform validation projects to be implemented by all Centers across BD-STEPS

A copy of the draft protocol is available upon request see *Section VII. Agency Contacts, Scientific / Research Contact(s)* Marcella Law to obtain a copy. The protocol will be finalized

by CDC in consultation with the recipients after the awards are made.

Table 1

Birth Defects included in BD-STEPS II Core
Spina bifida without anencephaly
Microcephaly if combined with brain anomaly
Holoprosencephaly
Anophthalmia/microphthalmia
Cataracts, glaucoma
Posterior eye defects
Anotia/microtia
Transposition of the great arteries (TGA)
Tetralogy of Fallot
Truncus arteriosus
Pulmonary atresia
Tricuspid atresia
Coarctation of aorta
Hypoplastic left heart syndrome
Anomalous pulmonary venous return
Cleft lip +/- cleft palate
Cleft palate
Esophageal atresia
Arthrogryposis in 2 or more joints
Transverse limb deficiency
Diaphragmatic hernia
Gastroschisis

Data reporting

Recipients are expected to collect, store, and transmit data in a standardized and secure manner with common elements mutually agreed upon by CDC and recipients. On a weekly basis, recipients will transfer contact information to the central interviewer using the CDC-provided

Secure Access Management Service. Recipients should be able to utilize .SQL and ACCESS databases in conjunction with their existing birth defects surveillance infrastructure.

Recipients will be responsible for compiling mailings to be sent to parents (e.g. introductory packets, thank you letters, various reminders, etc.); these mailings will include incentives as determined by the protocol. Recipients will not conduct the telephone interviews with the participants. The final thank you for all participants will notify them that they might be contacted at a later time for additional study components. Any information on the reportable diseases will be transferred to a central database at CDC. Any collected bloodspots will be stored by the recipients at a local facility.

Additional study components currently include an online questionnaire for a subset of participants with selected occupations, but further online components may be developed after discussion with the recipients.

Objectives/Outcomes (continued)

Component B. BD-STEPS stillbirth

To improve understanding of the causes of stillbirths that will inform public health prevention efforts, up to 2 study sites will focus on conducting research focused on stillbirths. There is little information on the causes of stillbirths and what impact having a stillbirth will have on future pregnancies. Significant racial disparities exist in the occurrence of stillbirths, with non-Hispanic Black women at much higher risk of having a stillbirth than non-Hispanic White women. Mothers over the age of 35 are also at greater risk for stillbirths. Working with CDC, two BD-STEPS I study sites have developed a supplementary phone interview with questions aimed specifically at elucidating causes of stillbirth.

- a. To ascertain, review and classify pregnancies that end in a stillbirth within the geographical region determined for BD-STEPS II.
- b. To collect information on exposures throughout pregnancy to modifiable risk factors via a maternal telephone interview.

Women who experienced a stillbirth and women who had babies born without birth defects (controls) will be invited to participate in the BD-STEPS II core interview and after completion, they will be invited to participate in a stillbirth interview to allow for the exploration of modifiable risk factors, such as sleeping position and maternal disease and medication use throughout pregnancy.

Project management

Recipients are expected to develop a management and staffing implementation plan for the proposed program. This plan should include the provision of evidence of legal authority to access data needed to accomplish the activities required by this NOFO and the recipient's application, including HIPAA and IRB requirements. The recipient will also provide evidence of legal authority to share identifiable, individual-level contact information with CDC and its contractors and individual-level data without names and addresses with other recipients of this cooperative agreement.

Data and specimen collection

The recipients are expected to identify pregnancies that end in a stillbirth without a birth defect from fetal death records, or delivery records and conduct clinical review for case confirmation. The recipients are expected to use the same region that is being covered for BD-STEPS II Core. The controls selected for BD-STEPS II Core will also be invited to participate in the stillbirth-specific interview.

Data reporting

Recipients are expected to collect, store, and transmit data in a standardized and secure manner with common elements mutually agreed upon by CDC and recipients. On a weekly basis, recipients will transfer contact information to the central interviewer using the CDC-provided Secure Access Management Service. Recipients will be responsible for compiling mailings to be sent to parents (e.g. introductory packets, thank you letters, various reminders, etc.); these mailings will include incentives as determined by the protocol. Recipients will not conduct the telephone interviews with the participants. The final thank you for all participants will notify them that they might be contacted at a later time for additional study components.

A copy of the draft protocol is available upon request see *Section VII. Agency Contacts, Scientific / Research Contact(s)* Marcella Law to obtain a copy. The protocol will be finalized by CDC in consultation with the recipients after the awards are made.

Timeline

Component A. BD-STEPS II Core & Component B. BD-STEPS Stillbirth

The anticipated general timeline for the project will consist of 3 phases over 5 years. The aim for Phase I is to initiate data collection as soon as possible.

Phase 1: Development (Months 1-6)

- Obtain IRB approval
- Develop the case and control ascertainment protocols
- Develop data sharing and publication agreements
- Develop and test database linkage to central tracking database
- Develop protocol to validate maternal self-reported medication use

Phase 2: Data collection and analyses (Months 7-54)

- Active case and control ascertainment
- Mailings to eligible cases and controls
- Case review and classification
- Conduct maternal interviews and collection of biologic samples
- Implement data validation pilot project (to include 1 year of births)
- Analyze pilot data and select method(s) to implement studywide
- Implement data validation procedures for self-reported medication use
- Data analyses, publications, and presentations

Phase 3: Complete study, ongoing publications and dissemination (Months 54-60)

- Complete ascertainment of cases and controls
- Complete mailings to eligible cases and controls
- Complete case review and classification
- Complete participant mailings and collection of biologic samples
- Conduct analyses, write manuscripts, prepare presentations

OMB will apply, the current OMB (#0920-0010) will expire on 2/29/2020.

References:

1. Dolk H. Preventing birth defects: The value of the NBDPS case-control approach. *Birth Defects Res A Clin Mol Teratol.* 2015.
2. Moore CA, Yoon PW, Edmonds LD, Erickson JD. Editorial perspectives from the founding CDC leadership of the National Birth Defects Prevention study. *Birth Defects Res A Clin Mol Teratol.* 2015.
3. Reefhuis J, Gilboa SM, Anderka M, Browne ML, Feldkamp ML, Hobbs CA, et al. The national birth defects prevention study: A review of the methods. *Birth Defects Res A Clin Mol Teratol.* 2015.
4. Yoon PW, Rasmussen SA, Lynberg MC, Moore CA, Anderka M, Carmichael SL, et al. The National Birth Defects Prevention Study. *Public Health Reports.* 2001;116 Suppl 1:32-40.
5. Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A, National Birth Defects Prevention S. Seeking causes: Classifying and evaluating congenital heart defects in etiologic studies. *Birth Defects Research.* 2007;79(10):714-27.
6. Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA, et al. Guidelines for case classification for the National Birth Defects Prevention Study. *Birth Defects Research.* 2003;67(3):193-201.
7. Rasmussen SA, Lammer EJ, Shaw GM, Finnell RH, McGehee RE, Jr., Gallagher M, et al. Integration of DNA sample collection into a multi-site birth defects case-control study. *Teratology.* 2002;66(4):177-84

Target Population

BD-STEPS II Core: The target population is women of childbearing potential, families contemplating pregnancy, public health care professionals, pregnant women, families of pregnancies affected by selected major birth defects, and families of children without selected major birth defects.

BD-STEPS stillbirth: The target population is women of childbearing potential, families contemplating pregnancy, public health care professionals, pregnant women, and families affected by stillbirths with and without selected major birth defects.

Collaboration/Partnerships

Recipients are expected to establish collaborations between state health departments, educational institutions, other recipients under this NOFO, and with the CDC. Ideally, research centers should be a meaningful collaboration between state health departments and academic centers. When appropriate, centers should collaborate and coordinate across state agencies and clinical settings for data collection not only for the ascertainment of birth defects, but also for the ascertainment of reportable infectious diseases. Recipients should work with CDC and other recipients to develop and implement standardized processes, methods, data collection, and other project activities. Recipients will provide members for key study committees (e.g., coordinating council, data sharing committee, clinicians committee, and a biologics committee). These committees have representatives from each site including the Georgia study site at CDC and will be charged to provide guidance and oversight over all aspects of BD-STEPS.

Evaluation/Performance Measurement

BD-STEPS II Core: The recipients will be expected to provide an annual progress report 90 days after the end of each budget period containing information on the following topics: 1) the timeliness of case identification and transfer to the central database measured from date of birth to date the introduction packet was sent out; 2) the quality of the provided address information measured as rate of initial contact success; 3) the speed with which additional data (case notes, contact information) requests are addressed; 4) the number and title of manuscripts prepared with BD-STEPS or NBDPS data; 5) the number and title of presentations given on BD-STEPS or NBDPS data; and 6) the number of junior researchers that were mentored each year and a description of activities undertaken.

BD-STEPS stillbirths: The recipients will be expected to provide an annual progress report 90 days after the end of each budget period containing information on the following topics: 1) the timeliness of case identification and transfer to the central database measured from date of delivery to date the introduction packet was sent out; 2) the number and titles of manuscripts on stillbirth specific research; and 3) the number and title of presentations given on stillbirth specific research.

Translation Plan

Recipients will be expected to analyze data and publish findings from BD-STEPS, as well as analyzing data previously collected for the NBDPS. All recipients will be provided access to the NBDPS pooled data upon local IRB approval and for use within the context of data sharing policies. This can include genetic analyses performed at local or external laboratories and funded through alternative funding sources. The main mode of dissemination of information to the public is expected to be through the production and publication of peer-reviewed scientific manuscripts. Each recipient will be expected to publish multiple manuscripts per year with a minimum of 10 published peer-reviewed manuscripts at the end of the 5 year project period. The coordinating council will establish public health priorities each year, and the centers will be expected to prioritize their research accordingly. A confidential abstract draft should be provided to CDC for each manuscript developed that was supported in part or whole by this cooperative agreement; the draft should be submitted to CDC at the time the manuscript is accepted for publication. Study results will be presented at national scientific conferences and

published in the peer-reviewed literature for dissemination to key stakeholders in order to facilitate translation into prevention messages.

Section II. Award Information

Funding Instrument Type:

Cooperative Agreement

A support mechanism used when there will be substantial Federal scientific or programmatic involvement. Substantial involvement means that, after award, scientific or program staff will assist, guide, coordinate, or participate in project activities.

Application Types Allowed:

New - An application that is submitted for funding for the first time. Includes multiple submission attempts within the same round.

Estimated Total Funding:

\$28,500,000

Component A: BD-STEPS II Core estimated total funding per year is \$5,300,000 with the average annual amount of each award of \$800,000 - \$900,000. Award Floor amount is \$700,000 and Award Ceiling amount is \$1,000,000.

Component B: BD-STEPS Stillbirth estimated total funding per year is \$400,000 with the average annual amount of each award of \$200,000. Award Floor amount is \$150,000 and Award Ceiling amount is \$250,000.

Anticipated Number of Awards:

6

We anticipate 5-7 total awards for Component A: BD-STEPS II Core. Of these funded awards, we are also anticipating 2 awards for Component B: BD-STEPS Stillbirth.

Awards issued under this NOFO are contingent on the availability of funds and submission of a sufficient number of meritorious applications.

Award Ceiling:

\$1,100,000 Per Budget Period

Award Floor:

\$700,000 Per Budget Period

Total Period of Performance Length:

5 year(s)

Throughout the Period of Performance, CDC's commitment to continuation of awards will depend on the availability of funds, evidence of satisfactory progress by the recipient (as documented in required reports), and CDC's determination that continued funding is in the best interest of the Federal government.

HHS/CDC grants policies as described in the HHS Grants Policy Statement (<https://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf>) will apply to the applications submitted and awards made in response to this NOFO.

Section III. Eligibility Information

1. Eligible Applicants

Eligibility Category:

Unrestricted (i.e., open to any type of entity above), subject to any clarification in text field entitled "Additional Information on Eligibility"

Additional Eligibility Category:

2. Foreign Organizations

Foreign Organizations are not eligible to apply.

Foreign components of U.S. Organizations are not eligible to apply.

For this announcement, applicants may not include collaborators or consultants from foreign institutions. All applicable federal laws and policies apply.

3. Special Eligibility Requirements

For an application to be considered, it must be responsive to the following special eligibility requirements:

Component A. BD-STEPS II CORE recipient:

1. Access to a pre-existing population-based birth defects surveillance system that can provide data on all birth defects listed in Table 1 and access to necessary data sources to ascertain liveborn control infants (i.e. vital records or birth hospital records) as evidenced by a letter from the State health department or other State or private organization.
2. Description of the selected birth population and geographic area which has to include 30,000 – 75,000 births annually as evidenced by a table listing the counties in the covered area, number of births in 2015 or 2016, and race/ethnic distribution.
3. Evidence of legal access to the birth defects surveillance system is required. If the applicant is not a State health department, inclusion of a letter or memorandum of understanding from the State health department confirming the applicant has access to the necessary data sources in order to ascertain case and control subjects.
4. Access to the state's National Electronic Disease Surveillance (NEDS) system for ascertainment of reportable infections as evidenced by a letter of support from the State's NEDS program.

Component B. BD-STEPS Stillbirth recipient:

1. Access to necessary data sources to ascertain stillborn infants (i.e. fetal death records or birth hospital records) as evidenced by a letter from the State health department or other State or private organization.
2. Description of the selected birth population and geographic area that includes 30,000 – 75,000 births annually as evidenced by a table listing the counties in the covered area,

number of births in 2015 or 2016, and race/ethnic distribution. This area has to be the same geographical area as described for Component A.

4. Justification for Less than Maximum Competition

Not Applicable.

5. Responsiveness

Evidence for these criteria must be presented in Appendix A of the application and may include:

Component A. BD-STEPS II Core

- Demonstrated access to a pre-existing population-based birth defects surveillance system that can provide data on all birth defects listed in Table 1 and ensuring access to data sources necessary to ascertain liveborn control infants (i.e. vital records or birth hospital records). Access can be demonstrated with a letter or other type of evidence from the State health department or other State organization or private organization ensuring access for the purposes and duration of the activities in this NOFO.
- A list or table of counties with number of annual births for 2015 or 2016 with race/ethnicity that confirm 30,000-75,000 births annually in the selected geographic area. Demonstrated access to the state birth defects surveillance system identified for the study. This can be in the form of a letter or memorandum of understanding from the State health department confirming access for the purpose and duration of the study. Applicant's information will be verified to published data.
- Demonstrated access to National Electronic Disease Surveillance (NEDS) system for ascertainment of reportable infections. This can be in form of a letter or other evidence from the State's NEDS program ensuring access to system for purposes and duration of the activities in this NOFO.

Component B. BD-STEPS stillbirth

- Demonstrated access, in the form of letters or other evidence from the State health department or other State organization or private organization, ensuring access to data sources necessary to ascertain stillborn infants (vital records or birth hospital records).
- A list or table of counties with number of annual births for 2015 or 2016 that confirm 30,000-75,000 births annually in the selected geographic area that will be the same geographical area as in Component A.

If your application is incomplete or non-responsive to the special eligibility requirements, HHS/CDC will consider the application non-responsive and it will not enter into the review process.

6. Required Registrations

Applicant organizations must complete the following registrations as described in the SF 424

(R&R) Application Guide to be eligible to apply for or receive an award. Applicants must have a valid Dun and Bradstreet Universal Numbering System (DUNS) number in order to begin each of the following registrations.

- (Foreign entities only): Special Instructions for acquiring a Commercial and Governmental Entity (NCAGE) Code: <https://eportal.nspa.nato.int/AC135Public/Docs/US%20Instructions%20for%20NSPA%20NCAGE.pdf>
- System for Award Management (SAM) – must maintain current registration in SAM (the replacement system for the Central Contractor Registration) to be renewed annually, <https://www.sam.gov/portal/SAM/#1>.
- [Grants.gov](https://www.Grants.gov)
- [eRA Commons](https://www.eRA Commons)

All applicant organizations must register with **Grants.gov**. Please visit www.Grants.gov at least 30 days prior to submitting your application to familiarize yourself with the registration and submission processes. The “one-time” registration process will take three to five days to complete. However, it is best to start the registration process at least two weeks prior to application submission.

All Program Directors/Principal Investigators (PD/PIs) **must** also work with their institutional officials to register with the **eRA Commons** or ensure their existing eRA Commons account is affiliated with the eRA Commons account of the applicant organization. **All registrations must be successfully completed and active before the application due date.** Applicant organizations are strongly encouraged to start the registration process at least four (4) weeks prior to the application due date.

7. Universal Identifier Requirements and System for Award Management (SAM)

All applicant organizations **must obtain** a DUN and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number is a nine-digit number assigned by Dun and Bradstreet Information Services. An AOR should be consulted to determine the appropriate number. If the organization does not have a DUNS number, an AOR should complete the [US D&B D-U-N-S Number Request Web Form](#) or contact Dun and Bradstreet by telephone directly at 1-866-705-5711 (toll-free) to obtain one. A DUNS number will be provided immediately by telephone at no charge. Note this is an organizational number. Individual Program Directors/Principal Investigators do not need to register for a DUNS number. Additionally, all applicant organizations must register in the **System for Award Management (SAM)**. Organizations must maintain the registration with current information at all times during which it has an application under consideration for funding by CDC and, if an award is made, until a final financial report is submitted or the final payment is received, whichever is later. SAM is the primary registrant database for the Federal government and is the repository into which an entity must provide information required for the conduct of business as a recipient. Additional information about registration procedures may be found at the SAM internet site at <https://www.sam.gov/index.html>.

If an award is granted, the recipient organization **must** notify potential sub-recipients that no organization may receive a subaward under the grant unless the organization has provided its

DUNS number to the recipient organization.

8. Eligible Individuals (Project Director/Principal Investigator) in Organizations/Institutions

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Project Director/Principal Investigator (PD/PI) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for HHS/CDC support.

9. Cost Sharing

This FOA does not require cost sharing as defined in the HHS Grants Policy Statement (<http://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf>).

10. Number of Applications

As defined in the HHS Grants Policy Statement, (<https://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf>), applications received in response to the same Notice of Funding Opportunity generally are scored individually and then ranked with other applications under peer review in their order of relative programmatic, technical, or scientific merit. HHS/CDC will not accept any application in response to this NOFO that is essentially the same as one currently pending initial peer review unless the applicant withdraws the pending application.

Only one application per institution (normally identified by having a unique DUNS number) is allowed for each Component for a potential of two applications under this NOFO.

One application for Component A: BD-STEPS II Core; and possibly one additional application for Component B: BD-STEPS stillbirths only if the institution is applying for funding under Component B.

Section IV. Application and Submission Information

1. Address to Request Application Package

Applicants must download the SF424 (R&R) application package associated with this funding opportunity from www.Grants.gov.

If access to the Internet is not available or if the applicant encounters difficulty accessing the forms on-line, contact the HHS/CDC Office of Grants Services (OGS) Technical Information Management Section (TIMS) staff at (770) 488-2700 or ogstims@cdc.gov for further instructions. Hours: Monday - Friday, 7am – 4:30pm U.S. Eastern Time. CDC Telecommunications for the hearing impaired or disabled is available at: TTY 1-888-232-6348.

2. Content and Form of Application Submission

It is critical that applicants follow the instructions in the SF424 (R&R) Application Guide <https://grants.nih.gov/grants/how-to-apply-application-guide/forms-e/general-forms-e.pdf> and here: <https://apply07.grants.gov/apply/forms/sample/SF424B-V1.1.pdf>, except where instructed in this Notice of Funding Opportunity to do otherwise. Conformance to the requirements in the

Application Guide is required and strictly enforced. Applications that are out of compliance with these instructions may be delayed or not accepted for review. The forms package associated with this NOFO includes all applicable components, mandatory and optional. Please note that some components marked optional in the application package are required for submission of applications for this NOFO. Follow the instructions in the SF 424 (R&R) Application Guide to ensure you complete all appropriate “optional” components. In conjunction with the SF424 (R&R) components, CDC grants applicants should also complete and submit additional components titled “PHS398.” Note the PHS398 should include assurances and certifications, additional data required by the agency for a complete application. While these are not identical to the PHS398 application form pages, the PHS398 reference is used to distinguish these additional data requirements from the data collected in the SF424 (R&R) components. A complete application to CDC will include SF424 (R&R) and PHS398 components. These forms can be downloaded from <http://grants.nih.gov/grants/funding/424/index.htm>.

Duplication of Efforts

Applicants are responsible for reporting if this application will result in programmatic, budgetary, or commitment overlap with another application or award (i.e. grant, cooperative agreement, or contract) submitted to another funding source in the same fiscal year. Programmatic overlap occurs when (1) substantially the same project is proposed in more than one application or is submitted to two or more funding sources for review and funding consideration or (2) a specific objective and the project design for accomplishing the objective are the same or closely related in two or more applications or awards, regardless of the funding source. Budgetary overlap occurs when duplicate or equivalent budgetary items (e.g., equipment, salaries) are requested in an application but already are provided by another source. Commitment overlap occurs when an individual’s time commitment exceeds 100 percent, whether or not salary support is requested in the application. Overlap, whether programmatic, budgetary, or commitment of an individual’s effort greater than 100 percent, is not permitted. Any overlap will be resolved by the CDC with the applicant and the PD/PI prior to award. Report Submission: The applicant must upload the report in Grants.gov under “Other Attachment Forms.” The document should be labeled: "Report on Programmatic, Budgetary, and Commitment Overlap.”

This NOFO is not to be utilized for basic birth defects case ascertainment.

3. Letter of Intent

Due Date for Letter of Intent: **[Insert 30 days from date of publication]**

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows CIO staff to estimate the potential review workload and plan the review.

By the date listed above and in Part 1. Overview Information, prospective applicants are asked

to submit a letter of intent that includes the following information:

Name of the Applicant

Descriptive title of proposed research

Name, address, and telephone number of the PD(s)/PI(s)

Descriptive title of each proposed Year 1 research project (up to 3)

Name, address and telephone number of the PI for each research project

Names of other key personnel

Participating institutions

Number and title of this funding opportunity

Letter of Intent should be e-mailed to:

Marcella Law

E-mail: mah7@cdc.gov

Scientific Program Official

Extramural Research Program Operations and Services

Centers for Disease Control and Prevention

4770 Buford Highway, NE, MS F-80

Atlanta, GA 30342

4. Required and Optional Components

A complete application has many components, both required and optional. The forms package associated with this NOFO in Grants.gov includes all applicable components for this NOFO, required and optional.

5. PHS 398 Research Plan Component

The SF424 (R&R) Application Guide includes instructions for applicants to complete a PHS 398 Research Plan that consists of 16 components. Not all 16 components of the Research Plan apply to all Notices of Funding Opportunities (NOFOs). Specifically, some of the following 16 components are for Resubmissions or Revisions only. See the SF 424 (R&R) Application Guide <https://grants.nih.gov/grants/how-to-apply-application-guide/forms-e/general-forms-e.pdf>

and here: <https://apply07.grants.gov/apply/forms/sample/SF424B-V1.1.pdf> for additional information. Please attach applicable sections of the following Research Plan components as directed in Part 2, Section 1 (Notice of Funding Opportunity Description). Follow the page limits stated in the SF 424 (R&R) unless otherwise specified in the NOFO. As applicable to and specified in the NOFO, the application should include the bolded headers in this section and should address activities to be conducted over the course of the entire project, including but not limited to:

- 1. Introduction to Application** (for Resubmission and Revision ONLY) - provide a clear description about the purpose of the proposed research and how it addresses the specific requirements of the NOFO.
- 2. Specific Aims** – state the problem the proposed research addresses and how it will result in public health impact and improvements in population health.
- 3. Research Strategy** – the research strategy should be organized under 3 headings: Significance, Innovation and Approach. Describe the proposed research plan, including staffing and timeline.
- 4. Inclusion Enrollment Report** (Renewal and Revision applications ONLY)
- 5. Progress Report Publication List** (for Continuation ONLY)

Human Subjects Section

- 6. Protection of Human Subjects**
- 7. Inclusion of Women and Minorities**
- 8. Targeted/Planned Enrollment Table** (for New Application ONLY)
- 9. Inclusion of Children**

Other Research Plan Sections

- 10. Vertebrate Animals**
- 11. Select Agent Research**
- 12. Multiple PD/PI Leadership Plan.**
- 13. Consortium/Contractual Arrangements**
- 14. Letters of Support**
- 15. Resource Sharing Plan(s)**
- 16. Appendix**

Component 4 (Inclusion Enrollment Report) applies only to Renewal and Revision applications for clinical research. Clinical research is that which is conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, and (d) development of new technologies). Follow the page limits in the [SF 424 \(R&R\) Application Guide](#) unless otherwise specified in the NOFO. All instructions in the SF424 (R&R) Application Guide <https://grants.nih.gov/grants/how-to-apply-application-guide/forms-e/general-forms-e.pdf> and here: <https://apply07.grants.gov/apply/forms/sample/SF424B-V1.1.pdf> must be followed along with

any additional instructions provided in the NOFO.

Applicants that plan to collect public health data must submit a Data Management Plan (DMP) in the Resource Sharing Plan section of the PHS 398 Research Plan Component of the application. A DMP is required for each collection of public health data proposed. Applicants who contend that the public health data they collect or create are not appropriate for release must justify that contention in the DMP submitted with their application for CDC funds. The DMP may be outlined in a narrative format or as a checklist but, at a minimum, should include:

- Descriptions of the data to be produced in the proposed project
- How access will be provided to the data (including provisions for protection of privacy, confidentiality, security, intellectual property, or other rights)
- Use of data standards that ensure all released data have appropriate documentation that describes the method of collection, what the data represent, and potential limitations for use
- Plans for archival and long-term preservation of the data, or explaining why long-term preservation and access cannot be justified

Examples of DMPs may be found here: University of California <https://dmp.cdlib.org/>, or USGS, <http://www.usgs.gov/datamanagement/plan/dmplans.php>

For those applicants applying for both components, a separate application for each Component of funding is required.

- Applicants should clearly indicate the Component for which they are applying and should include at the beginning of the title, the respective Component under which the application should be considered (i.e. Component A: BD-STEPS II Core; or Component B: BD-STEPS stillbirth).
- The applicant's Research Plan should address activities that will be conducted over the entire five-year project period and must include the following:

Component A. BD-STEPS II Core

1. Management and staffing plan

- a. Provide a staffing and management plan that defines the roles, responsibilities and qualifications of the applicant and each proposed partner. Roles should be closely linked with project activities and milestones and the unique role each partner will play. Minimum personnel should include: PI; study coordinator; epidemiologist(s) (at least 20% effort); clinician(s) (at least 1 clinical geneticist and 1 pediatric cardiologist at a minimum of 5% effort each)
- b. Provide evidence of birth defects research capacity as demonstrated by staff expertise, including senior staff with a published track record on birth defects public health research in high impact journals and junior staff being mentored.
- c. Provide plans for maintaining confidentiality and privacy of all participants and adherence to all provisions of the BD-STEPS Certificate of Confidentiality.
- d. Provide evidence of ability to manage study protocol aspects that includes:

- i. Ability to maintain the awardee's access to the study's central tracking database;
- ii. Ability to adhere to the standard protocol with regards to all participant consents, including interview, blood spot, and infectious disease linkage;
- iii. Ability to enter the necessary contact and clinical information into the study's central tracking database; and
- iv. Ability to develop methods to decrease time between ascertainment of study subject and entry into the tracking database.
- e. If award funds will be used to pay for travel costs associated with attending program meetings or presenting at national scientific meetings, those costs must be included in the budget and justified as supporting this project. At least 2 persons should attend an annual 2-day in-person meeting in Atlanta.
- f. Provide evidence of ability to defer to central IRB as required by the Common Rule, or provide a copy of the law preventing deferral.

2. Partnership and collaboration

- a. Provide documentation demonstrating partnership with the State Health Department and ability to ascertain reportable disease status for case and control mothers and infants from the National Electronic Disease Surveillance system.
- b. Provide ability to access vital records and birth hospital logs. Applicants must have access to vital records for 1) verifying study eligibility, e.g., birth residence requirements, fetal deaths, birth defect status, and 2) contacting eligible participants
- c. Provide documentation on ascertainment of prenatally diagnosed cases (unless this is specifically prohibited by state law and that fact should be stated within the narrative), and how these cases contribute to the proposed defects.
- d. Provide a description of collaborative projects with birth defects surveillance systems since 1/1/2010. Applicants may provide descriptions of any collaborative projects they feel incorporates some form of birth defects surveillance data. However, BD-STEPS includes only data from active, population-based surveillance systems. Demonstration of previous collaborations with active, population-based surveillance systems are most relevant to the current NOFO. In addition, previous collaboration with the surveillance system that will be the source for cases for the applicant should be a focus of this description.
- e. Describe your willingness and ability to assume active participation and take leadership roles in BD-STEPS committees and workgroups, conference calls, and in-person meetings.

3. Research activities

- a. Describe any experience in implementing studies in population-based birth defects epidemiological research that is relevant to your ability to successfully implement BD-STEPS II Core and support its scientific goals. Please include:

- i. Descriptions of scope, complexity, and size (including final sample size) of previous studies;
 - ii. Descriptions of measures of implementation success from previous studies (e.g., research recruitment rates; birth defects surveillance rates in line with other published estimates; quality control measures; estimates of data collection completeness on each enrolled participant; representativeness and/or generalizability of research sample and results; timeliness of study implementation);
 - iii. Professional reports, publications and presentations (titles and references; not actual documents); and
 - iv. Description of relevance of previous studies to birth defects research needs (i.e., significance of knowledge gaps that were filled).
- b. Describe your study catchment area and the corresponding birth population size in the area in 2015 or 2016 (must include 30,000 – 75,000 births annually). If you are a BD- STEPS I site, describe the overlap between the BD- STEPS I catchment area and the proposed BD- STEPS II catchment area. Describe the race/ethnicity and sociodemographic characteristics of your proposed catchment area study population and how they compare to the state if the area is not statewide.
 - c. Provide evidence of experience with analyzing and disseminating surveillance data generated by the surveillance system.
 - d. Provide evidence to demonstrate a high sensitivity of case ascertainment and ability to comply with all BD- STEPS case definitions (described in the protocol available From Marcella Law) . Each recipient must support local classification of eligible birth defects by a clinical geneticist, in addition to clinical review of cases in pooled data by clinical geneticists (pediatric cardiologists for heart defects) estimated to be around 200 cases per year per site.
 - e. Provide evidence of ability to ascertain all of the defects in the current defect list with high sensitivity. Prevalence data for 2012-2015 for the defects should be included (see Table 1).
 - f. Provide a detailed description of your site-specific plan for implementing BD- STEPS II ascertainment, recruitment and data collection procedures. Describe specific methods to implement BD- STEPS II in order to send at least 80% of all eligible cases and controls to the central interviewer by 10 months after birth. Evidence of this ability should include demonstration of rapid case ascertainment for other research studies.
 - g. Provide plans for obtaining information on infections from the state National Electronic Disease Surveillance system for infections 2 years before and during pregnancy.
 - h. Provide plans to evaluate the surveillance methodology used that can lead to improvement in timeliness and improvement or expansion of case ascertainment.
 - i. Provide plans for developing and implementing a pilot project to validate maternal self-reported medication use during pregnancy.
 - j. Describe your ability to analyze data generated by epidemiological research. Applicant must demonstrate willingness and ability to assess data using quality

control methods to maintain BD-STEPS standards for data collection and analyses.

k. Describe your ability to handle data security and confidentiality. Provide approach for maintaining security, confidentiality and privacy of all participant data.

l. Describe your ability and willingness to support the BD-STEPS II data management, analysis and reporting plans.

i. Recipient must be able to use and support Access and .SQL data systems.

ii. Recipient must conduct site-specific data cleaning tasks in a timely manner, including tasks related to preparation of analytic data.

iii. Recipient must submit contact information within the deadline to the central interviewing facility.

iv. Recipient must contribute all site-specific data to BD-STEPS II clinical dataset.

v. Recipient must adhere to existing BD-STEPS Data Sharing Guidelines for analysis, presentation, publication, data release, and data return.

m. It is expected that a minimum of 10 manuscripts will be developed by each recipient.

4. Translation plan

a. Describe your plans to use research results to fill public health gaps. Provide a brief description of recent, high impact birth defects research manuscripts and presentations by key personnel. The description should include collaboration, analytic approach, and potential public health impact, or how it contributes to our understanding of the causes of major birth defects and provide opportunities for prevention/intervention.

Component B. BD-STEPS stillbirth

1. Management and staffing plan

a. Provide a staffing and management plan that defines the roles, responsibilities and qualifications of the applicant and each proposed partner. Roles should be closely linked with project activities and milestones and the unique role each partner will play. Minimum personnel should include: PI; study coordinator; epidemiologist(s) (at least 20% effort).

b. Provide evidence of stillbirth research capacity as demonstrated by staff expertise, including senior staff with a published track record on stillbirth public health research in high impact journals and junior staff being mentored.

c. Provide plans for maintaining confidentiality and privacy of all participants and adherence to all provisions of the BD-STEPS Certificate of Confidentiality.

d. Provide evidence of ability to manage study data that includes:

i. Ability to maintain the recipient's access to the study's central tracking database;

ii. Ability to enter the necessary contact and clinical information into the study's central tracking database; and

iii. Ability to develop methods to decrease time between ascertainment of study subject and entry into the tracking database.

e. If award funds will be used to pay for travel costs associated with attending program meetings or presenting at national scientific meetings, those costs must be included in the budget and justified as supporting this project. At least 2 persons should attend an annual 2-day in-person meeting in Atlanta.

f. Provide evidence of ability to defer to central IRB as required by the Common Rule, or provide a copy of the law preventing deferral.

2. Partnership and collaboration

a. Provide ability to access vital records and birth hospital logs. Applicants must have access to vital records for 1) verifying study eligibility, e.g., birth residence requirements, fetal deaths, birth defect status, and 2) contacting eligible participants.

b. Describe your willingness and ability to assume active participation and take leadership roles in BD-STEPS committees and workgroups, conference calls, and in-person meetings.

3. Research activities

a. Describe any experience in implementing studies in population-based stillbirth epidemiological research that is relevant to your ability to successfully implement BD-STEPS Stillbirth and support its scientific goals. Please include:

i. Descriptions of scope, complexity, and size (including final sample size) of previous studies;

ii. Descriptions of measures of implementation success from previous studies (e.g., research recruitment rates; stillbirth surveillance rates in line with other published estimates; quality control measures; estimates of data collection completeness on each enrolled participant; representativeness and/or generalizability of research sample and results; timeliness of study implementation);

iii. Professional reports, publications and presentations (titles and references; not actual documents); and

iv. Description of relevance of previous studies to stillbirth research needs (i.e., significance of knowledge gaps that were filled).

b. Provide plans to evaluate the stillbirth surveillance methodology used that can lead to improvement in timeliness and improvement of case ascertainment.

c. Provide a detailed description of your site-specific plan for implementing BD-STEPS Stillbirth ascertainment, recruitment and data collection procedures. Describe specific methods to implement BD-STEPS stillbirth in order to identify at least 80% of all eligible cases and controls by 10 months after birth. Evidence of this ability should include

demonstration of rapid case ascertainment for other research studies.

- d. Describe your ability to analyze data generated by epidemiological research. Applicant must demonstrate willingness and ability to assess data using quality control methods to maintain BD-STEPS standards for data collection and analyses.
- e. Describe your ability to handle data security and confidentiality. Provide approach for maintaining security, confidentiality and privacy of all participant data.
- f. Describe your ability and willingness to support the BD-STEPS Stillbirth data management, analysis and reporting plans.
 - i. Recipient must be able to use and support Access and .SQL data systems;
 - ii. Recipient must conduct site-specific data cleaning tasks in a timely manner, including tasks related to preparation of analytic data;
 - iii. Recipient must contribute all site-specific data to BD-STEPS Stillbirth pooled dataset;
 - iv. Recipient must adhere to existing BD-STEPS Data Sharing Guidelines for analysis, presentation, publication, data release, and data return.

Translation plan

- a. Describe your plans to use research results to fill public health gaps. Provide a brief description of recent, high impact stillbirth research manuscripts and presentations by key personnel. The description should include collaboration, analytic approach, and potential public health impact, or how it contributes to our understanding of the causes of stillbirth and provide opportunities for prevention/intervention.

6. Appendix

Do not use the appendix to circumvent page limits. A maximum of 10 PDF documents are allowed in the appendix. Additionally, up to 3 publications may be included that are not publically available. Follow all instructions for the Appendix as described in the SF424 (R&R) Application Guide.

As applicable, applicants can provide links to publications and other information in lieu of attaching pdf documents.

7. Page Limitations

All page limitations described in this individual NOFO must be followed. For this specific NOFO, the Research Strategy component of the Research Plan narrative is limited to 25 pages. Supporting materials for the Research Plan narrative included as appendices may not exceed 10 PDF files with a maximum of 30 pages for all appendices.

8. Format for Attachments

Designed to maximize system-conducted validations, multiple separate attachments are required for a complete application. When the application is received by the agency, all submitted forms

and all separate attachments are combined into a single document that is used by peer reviewers and agency staff. Applicants should ensure that all attachments are uploaded to the system. **CDC requires all text attachments to the Adobe application forms be submitted as PDFs and that all text attachments conform to the agency-specific formatting requirements noted in the SF424 (R&R) Application Guide** <https://grants.nih.gov/grants/how-to-apply-application-guide/forms-e/general-forms-e.pdf> and here: <https://apply07.grants.gov/apply/forms/sample/SF424B-V1.1.pdf>.

9. Submission Dates & Times

Part I. Overview Information contains information about Key Dates. Applicants are encouraged to submit in advance of the deadline to ensure they have time to make any application corrections that might be necessary for successful submission.

Organizations must submit applications via [Grants.gov](https://www.grants.gov) (<https://www.grants.gov>), the online portal to find and apply for grants across all Federal agencies. The eRA Commons systems retrieve the application from Grants.gov and check the application against CDC business rules. If no errors are found, the application will be assembled in the eRA Commons for viewing by the applicant before moving on for further CDC processing.

If errors are found, the applicant will be notified in the eRA Commons. They must make required changes to the local copy of their application and submit again through Grants.gov.

Applicants are responsible for viewing their application in the eRA Commons to ensure accurate and successful submission.

Once you can see your application in the Commons, be sure to review it carefully as this is what the reviewer will see. Applicants must then complete the submission process by tracking the status of the application in the eRA Commons (http://grants.nih.gov/grants/guide/url_redirect.htm?id=11123).

Information on the submission process is provided in the SF424 (R&R) Application Guide.

Note: HHS/CDC grant submission procedures do not provide a period of time beyond the grant application due date to correct any error or warning notices of noncompliance with application instructions that are identified by Grants.gov or eRA systems (i.e. error correction window).

The application package is not complete until it has passed the Grants.gov/eRA Commons validation process. This process and email notifications of receipt, validation or rejection may take two (2) business days.

Applicants are strongly encouraged to allocate additional time prior to the submission deadline to submit their applications and to correct errors identified in the validation process. Applicants are encouraged also to check the status of their application submission to determine if the application packages are complete and error-free. Applicants who encounter system errors when submitting their applications must attempt to resolve them by contacting the Grants.gov Contact Center (1-800-518-4726; support@grants.gov). If the system errors cannot be resolved, applicants must contact TIMS at 770-488-2700; ogstims@cdc.gov for guidance at least 3 calendar days before the deadline date.

After submission of your application package, applicants will receive a “submission receipt” email generated by Grants.gov. Grants.gov will then generate a second e-mail message to applicants which will either validate or reject their submitted application package. This validation process may take as long as two (2) business days. A third and final e-mail message is generated once the applicant’s application package has passed

validation and the grantor has confirmed receipt of the application.

Unsuccessful Submissions: If an application submission was unsuccessful, *the applicant* must:

1. Track his/her submission and verify the submission status (tracking should be done initially regardless of rejection or success).
 - a. If the status states “*rejected*,” do #2a or #2b.
2. Check his/her emails from both Grants.gov and eRA Commons for rejection notices.
 - a. If the deadline has passed, he/she should email the Grant Management Specialist listed in the NOFO (ogstims@cdc.gov) explaining why the submission failed. b. If there is time before the deadline, he/she should correct the problem(s) and resubmit as soon as possible.

Due Date for Applications: **02/22/2018**

Electronically submitted applications must be submitted no later than 5:00 p.m., ET, on the listed application due date.

10. Intergovernmental Review (E.O. 12372)

This initiative is not subject to intergovernmental review ([http:// www. whitehouse.gov/ omb/ grants_ spoc](http://www.whitehouse.gov/omb/grants_spoc)).

11. Funding Restrictions

All HHS/CDC awards are subject to the federal regulations, 45 CFR 75, terms and conditions, and other requirements described in the HHS Grants Policy Statement. Pre-award costs may be allowable as an expanded authority, but only if authorized by CDC. In accordance with the United States Protecting Life in Global Health Assistance policy, all non-governmental organization (NGO) applicants acknowledge that foreign NGOs that receive funds provided through this award, either as a prime recipient or subrecipient, are strictly prohibited, regardless of the source of funds, from performing abortions as a method of family planning or engaging in any activity that promotes abortion as a method of family planning, or to provide financial support to any other foreign non-governmental organization that conducts such activities. See Additional Requirement (AR) 35 for applicability (<https://www.cdc.gov/grants/additionalrequirements/ar-35.html>).

For more information on expanded authority and pre-award costs, go to:

<https://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf>.

CDC requires that mechanisms for, and cost of, public health data sharing be included in grants, cooperative agreements, and contracts. The cost of sharing or archiving public health data may also be included as part of the total budget requested for first-time or continuation awards.

Fulfilling the data-sharing requirement must be documented in a Data Management Plan (DMP) that is developed during the project planning phase prior to the initiation of generating or collecting public health data and must be included in the Resource Sharing Plan(s) section of the PHS398 Research Plan Component of the application.

Applicants who contend that the public health data they collect or create are not appropriate for

release must justify that contention in the DMP submitted with their application for CDC funds (for example, privacy and confidentiality considerations, embargo issues).

Recipients who fail to release public health data in a timely fashion will be subject to procedures normally used to address lack of compliance (for example, reduction in funding, restriction of funds, or award termination) consistent with 45 CFR 74.62 or other authorities as appropriate. For further information, please

see: <https://www.cdc.gov/grants/additionalrequirements/ar-25.html> for revised AR-25.

Funds will be restricted until:

- IRB and OMB/PRA (if needed) approvals are obtained.
- Human Subjects Education Requirement documentation is provided for any new key personnel or other significant contributors involved in the design or conduct or research involving human subjects.

Applicants are advised that any activities involving standard information collection (i.e., surveys, questionnaires, data requests, etc.) from 10 or more non-federal individual/entities are subject to Paperwork Reduction Act (PRA) requirements and may require the CDC to coordinate an OMB/PRA approval request).

Reimbursement of pre-award costs is not allowed. All HHS/CDC awards are subject to the terms and conditions, cost principles, and other requirements described in the HHS Grants Policy Statement. Pre-award costs may be allowable as an expanded authority, but only if authorized by CDC.

For more information on expanded authority and pre-award costs, go to: <http://www.hhs.gov/asfr/ogapa/aboutog/hhsgps107.pdf> or speak with your Grants Management Specialist (GMS).

12. Other Submission Requirements and Information

Application Submission

Applications must be submitted electronically following the instructions described in the SF 424 (R&R) Application Guide. **PAPER APPLICATIONS WILL NOT BE ACCEPTED.**

Applicants must complete all required registrations before the application due date.

Section III.6 "Required Registrations" contains information about registration.

For assistance with your electronic application or for more information on the electronic submission process, visit Applying Electronically (http://grants.nih.gov/grants/guide/url_redirect.htm?id=11144).

Important reminders: All PD/PIs must include their eRA Commons ID in the Credential field of the Senior/Key Person Profile Component of the SF 424(R&R) Application Package. Failure to register in the Commons and to include a valid PD/PI Commons ID in the credential field will prevent the successful submission of an electronic application to CDC.

The applicant organization must ensure that the DUNS number it provides on the

application is the same number used in the organization's profile in the eRA Commons and for the System for Award Management (SAM). Additional information may be found in the SF424 (R&R) Application Guide.

If the applicant has an FWA number, enter the 8-digit number. Do not enter the letters "FWA" before the number. If a Project/Performance Site is engaged in research involving human subjects, the applicant organization is responsible for ensuring that the Project/Performance Site operates under and appropriate Federal Wide Assurance for the protection of human subjects and complies with 45 CFR Part 46 and other CDC human subject related policies described in Part II of the SF 424 (R&R) Application Guide and in the HHS Grants Policy Statement.

See more resources to avoid common errors and submitting, tracking, and viewing applications: http://grants.nih.gov/grants/ElectronicReceipt/avoiding_errors.htm or http://grants.nih.gov/grants/ElectronicReceipt/submit_app.htm

Upon receipt, applications will be evaluated for completeness by the CDC Office of Grants Services (OGS) and responsiveness by OGS and the Center, Institute or Office of the CDC. Applications that are incomplete and/or nonresponsive will not be reviewed.

Section V. Application Review Information

1. Criteria

Only the review criteria described below will be considered in the review process. As part of the CDC mission (<http://www.cdc.gov/about/organization/mission.htm>), all applications submitted to the CDC in support of public health research are evaluated for scientific and technical merit through the CDC peer review system.

Overall Impact

Reviewers will provide an overall impact/priority score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the project proposed).

Scored Review Criteria

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

Significance

Does the project address an important problem or a critical barrier to progress in the field? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Component A. BD-STEPS II Core

- Does the work address a scientific problem of great importance to public health research and/or practice?
- Will the work be influential in that it will lead others to investigate the problem, open new areas of research, or change the scientific approach or public health practice, and how will this improve and be of value to public health?

Component B. BD-STEPS stillbirth

- Does the work address a scientific problem of great importance to public health research and/or practice?
- Will the work be influential in that it will lead others to investigate the problem, open new areas of research, or change the scientific approach or public health practice, and how will this improve and be of value to public health?

Investigator(s)

Are the PD/PIs, collaborators, and other researchers well suited to the project? Have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

Component A. BD-STEPS II Core

- Do the investigators have a successful track record in public health research?
- Do the proposed staff include at least a project coordinator, data manager, 5% FTE clinical geneticist, 5% pediatric cardiologist and 20% FTE epidemiologist?
- Is there evidence of past collaborations with the proposed research team?
- Have previous research results provided high quality outputs (as evidence by publications in high impact journals) and contributed to improvements in public health practice and population health?
- Are the investigators mentoring or planning to mentor junior researchers in the field of birth defects epidemiology?
- Has sufficient abstracting staff been identified to enable the timely addressing of any requests for additional clinical or contact information?
- Has sufficient project coordination staff been identified to complete the mailings in a timely manner?
- Do the investigators have experience specifically in birth defects research?
- Do the investigators have a collaborative working relationship with the team responsible for birth defects surveillance in their study health department?
- Do the investigators have a collaborative working relationship with the reportable disease surveillance in their State Health Department?

Component B. BD-STEPS stillbirth

- Do the investigators have a successful track record in public health research?
- Do the proposed staff include at least a project coordinator, data manager, 5% FTE obstetrician, and 5% perinatal pathologist and an epidemiologist?
- Is there evidence of past collaborations with the proposed research team?
- Have previous research results provided high quality outputs (as evidence by publications in high impact journals) and contributed to improvements in public health practice and population health?
- Are the investigators mentoring or planning to mentor junior researchers in the field of stillbirth epidemiology?
- Has sufficient abstracting staff been identified to enable the timely addressing of any requests for additional clinical or contact information?
- Has sufficient project coordination staff been identified to complete the mailings in a timely manner?
- Do the investigators have experience specifically in birth defects research?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Component A. BD-STEPS II Core

- Do the proposed methods build on previous experience with birth defects research and provide a high likelihood of success in identifying new modifiable risk factors?

Component B. BD-STEPS stillbirth

- Do the proposed methods build on previous experience with stillbirth research and provide a high likelihood of success in identifying new modifiable risk factors?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? If the project involves clinical research, are there plans for 1) protection of human subjects from research risks, and 2) inclusion of minorities and members of both sexes/genders, as well as the inclusion of children, justified in terms of the scientific goals and research

strategy proposed?

Component A. BD-STEPS II Core

- Are there plans for 1) protection of human subjects from research risks, and 2) inclusion of vulnerable populations justified in terms of the scientific goals and research strategy proposed?
- Are the overall strategy, methodology, and analyses well reasoned and appropriate to accomplish the specific aims of the project?
- Is the applicant able to defer to a central IRB?
- Has the applicant documented how they will meet the case ascertainment sensitivity and timeliness requirements of the project?
- Has the applicant provided evaluation metrics for the project that are SMART (specific, measurable, achievable, realistic, time phased)?

Component B. BD-STEPS stillbirth

- Are there plans for 1) protection of human subjects from research risks, and 2) inclusion of vulnerable populations justified in terms of the scientific goals and research strategy proposed?
- Are the overall strategy, methodology, and analyses well reasoned and appropriate to accomplish the specific aims of the project?
- Has the applicant documented how they will meet the case ascertainment sensitivity and timeliness requirements of the project?
- Has the applicant provided evaluation metrics for the project that are SMART (specific, measurable, achievable, realistic, time phased)?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Component A. BD-STEPS II Core

- Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements such as a collaboration between an academic center and a health department?
- Is there sufficient existing support for the birth defects surveillance system to warrant timely and complete ascertainment of cases?
- Is there documented collaboration between the State health department and the recipient (if other than State Health Department)?

- Will the recipient be able to train and mentor students and junior researchers in the field of birth defects epidemiology?

Component B. BD-STEPS stillbirth

- Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements such as a collaboration between an academic center and a health department?
- Is there sufficient existing support for the vital records system to warrant timely and complete ascertainment of cases?
- Is there documented collaboration between the State health department and the recipient (if other than State Health Department)?
- Will the recipient be able to train and mentor students and junior researchers in the field of stillbirth epidemiology?

2. Additional Review Criteria

As applicable for the project proposed, *reviewers will evaluate* the following additional items while determining scientific and technical merit, and in providing an overall impact/priority score, but *will not give separate scores* for these items.

Protections for Human Subjects

If the research involves human subjects but does not involve one of the six categories of research that are exempt under [45 CFR Part 46](#), the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the HHS/CDC Requirements under AR-1 Human Subjects Requirements (<http://www.cdc.gov/grants/additionalrequirements/index.html>).

If your proposed research involves the use of human data and/or biological specimens, you must provide a justification for your claim that no human subjects are involved in the Protection of Human Subjects section of the Research Plan.

Inclusion of Women, Minorities, and Children

When the proposed project involves clinical research, the committee will evaluate the proposed plans for inclusion of minorities and members of both genders, as well as the inclusion of children. For additional information on review of the Inclusion section, please refer to the policy on the Inclusion of Women and Racial and Ethnic Minorities in Research (https://www.cdc.gov/maso/Policy/Policy_women.pdf) and the policy on the Inclusion of

Persons Under 21 in Research(<https://www.cdc.gov/maso/Policy/policy496.pdf>).

Vertebrate Animals

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following five points: 1) proposed use of the animals, and species, strains, ages, sex, and numbers to be used; 2) justifications for the use of animals and for the appropriateness of the species and numbers proposed; 3) adequacy of veterinary care; 4) procedures for limiting discomfort, distress, pain and injury to that which is unavoidable in the conduct of scientifically sound research including the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices; and 5) methods of euthanasia and reason for selection if not consistent with the AVMA Guidelines on Euthanasia. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section (<https://grants.nih.gov/grants/olaw/VASchecklist.pdf>).

Biohazards

Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Dual Use Research of Concern

Reviewers will identify whether the project involves one of the agents or toxins described in the US Government Policy for the Institutional Oversight of Life Sciences Dual Use Research of Concern, and, if so, whether the applicant has identified an IRE to assess the project for DURC potential and develop mitigation strategies if needed.

For more information about this Policy and other policies regarding dual use research of concern, visit the U.S. Government Science, Safety, Security (S3) website at:

<http://www.phe.gov/s3/dualuse>. Tools and guidance for assessing DURC potential may be found at: <http://www.phe.gov/s3/dualuse/Pages/companion-guide.aspx>.

3. Additional Review Considerations

As applicable for the project proposed, reviewers will consider each of the following items, but *will not give scores* for these items, and should not consider them in providing an overall impact/priority score.

Resource Sharing Plan(s)

HHS/CDC policy requires that recipients of grant awards make research resources and data readily available for research purposes to qualified individuals within the scientific community

after publication. Please see: <https://www.cdc.gov/grants/additionalrequirements/ar-25.html>

New additional requirement: CDC requires recipients for projects and programs that involve data collection or generation of data with federal funds to develop and submit a Data Management Plan (DMP) for each collection of public health data.

Investigators responding to this notice of funding opportunity should include a detailed DMP in the Resource Sharing Plan(s) section of the PHS 398 Research Plan Component of the application. The [AR-25](#) outlines the components of a DMP and provides additional information for investigators regarding the requirements for data accessibility, storage, and preservation.

The DMP should be developed during the project planning phase prior to the initiation of collecting or generating public health data and will be submitted with the application. The submitted DMP will be evaluated for completeness and quality at the time of submission.

The DMP should include, at a minimum, a description of the following:

- Type of data to be produced in the proposed project;
- Mechanisms for providing access to and sharing of the data (including provisions for the protection of privacy, confidentiality, security, intellectual property, or other rights);
- Use of data standards that ensure all released data have appropriate documentation that describes the method of collection, what the data represent, and potential limitations for use; and
- Plans for archiving and long-term preservation of the data, or explaining why long-term preservation and access are not justified.

Applications submitted without the required DMP may be deemed ineligible for award unless submission of DMP is deferred to a later period depending on the type of award, in which case, funding restrictions may be imposed pending submission and evaluation.

Budget and Period of Support

Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research. The applicant can obtain guidance for completing a detailed justified budget on the CDC website, at the following Internet address: <http://www.cdc.gov/grants/interestedinapplying/applicationresources.html>

The budget can include both direct costs and indirect costs as allowed.

Indirect costs could include the cost of collecting, managing, sharing and preserving data.

Indirect costs on grants awarded to foreign organizations and foreign public entities and performed fully outside of the territorial limits of the U.S. may be paid to support the costs of compliance with federal requirements at a fixed rate of eight percent of modified total direct costs exclusive of tuition and related fees, direct expenditures for equipment, and subawards in excess of \$25,000. Negotiated indirect costs may be paid to the American University, Beirut, and the World Health Organization.

Indirect costs on training grants are limited to a fixed rate of eight percent of MTDC exclusive of tuition and related fees, direct expenditures for equipment, and sub-awards in excess of \$25,000.

If requesting indirect costs in the budget, a copy of the indirect cost rate agreement is required. Include a copy of the current negotiated federal indirect cost rate agreement or cost allocation plan approval letter.

The applicant can obtain guidance for completing a detailed justified budget on the CDC website, at the following Internet address: <https://www.cdc.gov/grants/documents/Budget-Preparation-Guidance.docx>

4. Review and Selection Process

Applications will be evaluated for scientific and technical merit by an appropriate peer review group, in accordance with CDC peer review policy and procedures, using the stated review criteria.

As part of the scientific peer review, all applications:

- Will undergo a selection process in which all responsive applications will be discussed and assigned an overall impact/priority score.
- Will receive a written critique.

Applications will be assigned to the appropriate HHS/CDC Center, Institute, or Office. Applications will compete for available funds with all other recommended applications submitted in response to this NOFO. Following initial peer review, recommended applications will receive a second level of review. The following will be considered in making funding decisions:

- Scientific and technical merit of the proposed project as determined by scientific peer review.
- Availability of funds.
- Relevance of the proposed project to program priorities.
- Racial/ethnic diversity of the proposed population for study.
- Annual number of live births in the proposed geographical area.

Review of risk posed by applicants.

Prior to making a Federal award, CDC is required by 31 U.S.C. 3321 and 41 U.S.C. 2313 to review information available through any OMB-designated repositories of government-wide eligibility qualification or financial integrity information as appropriate. See also suspension and debarment requirements at 2 CFR parts 180 and 376.

In accordance 41 U.S.C. 2313, CDC is required to review the non-public segment of the OMB-designated integrity and performance system accessible through SAM (currently the Federal Recipient Performance and Integrity Information System (FAPIIS)) prior to making a Federal award where the Federal share is expected to exceed the simplified acquisition threshold, defined in 41 U.S.C. 134, over the period of performance. At a minimum, the information in the system for a prior Federal award recipient must demonstrate a satisfactory record of executing programs or activities under Federal grants, cooperative agreements, or procurement awards; and integrity and business ethics. CDC may make a Federal award to a recipient who does not fully meet these standards, if it is determined that the information is not relevant to the current Federal award under consideration or there are specific conditions that can appropriately mitigate the effects of the non-Federal entity's risk in accordance with 45 CFR

§75.207.

CDC's framework for evaluating the risks posed by an applicant may incorporate results of the evaluation of the applicant's eligibility or the quality of its application. If it is determined that a Federal award will be made, special conditions that correspond to the degree of risk assessed may be applied to the Federal award. The evaluation criteria is described in this notice of funding opportunity.

In evaluating risks posed by applicants, CDC will use a risk-based approach and may consider any items such as the following:

- (1) Financial stability;
- (2) Quality of management systems and ability to meet the management standards prescribed in this part;
- (3) History of performance. The applicant's record in managing Federal awards, if it is a prior recipient of Federal awards, including timeliness of compliance with applicable reporting requirements, conformance to the terms and conditions of previous Federal awards, and if applicable, the extent to which any previously awarded amounts will be expended prior to future awards;
- (4) Reports and findings from audits performed under subpart F 45 CFR 75 or the reports and findings of any other available audits; and
- (5) The applicant's ability to effectively implement statutory, regulatory, or other requirements imposed on non-Federal entities.

CDC must comply with the guidelines on government-wide suspension and debarment in 2 CFR part 180, and require non-Federal entities to comply with these provisions. These provisions restrict Federal awards, subawards and contracts with certain parties that are debarred, suspended or otherwise excluded from or ineligible for participation in Federal programs or activities.

5. Anticipated Announcement and Award Dates

After the peer review of the application is completed, the PD/PI will be able to access his or her Summary Statement (written critique) and other pertinent information via the eRA Commons.

Section VI. Award Administration Information

1. Award Notices

Any applications awarded in response to this NOFO will be subject to the DUNS, SAM Registration, and Transparency Act requirements. If the application is under consideration for funding, HHS/CDC will request "just-in-time" information from the applicant as described in the HHS Grants Policy Statement (<https://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf>).

A formal notification in the form of a Notice of Award (NoA) will be provided to the applicant organization for successful applications. The NoA signed by the Grants Management Officer is the authorizing document and will be sent via email to the recipient's business official.

Recipients must comply with any funding restrictions as described in Section IV.11. Funding

Restrictions. Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NoA are at the recipient's risk. These costs may be allowable as an expanded authority, but only if authorized by CDC.

2. CDC Administrative Requirements

Overview of Terms and Conditions of Award and Requirements for Specific Types of Grants

Administrative and National Policy Requirements, Additional Requirements (ARs) outline the administrative requirements found in 45 CFR Part 75 and the HHS Grants Policy Statement and other requirements as mandated by statute or CDC policy. CDC programs must indicate which ARs are relevant to the NOFO. All NOFOs from the Center for Global Health must include AR-35. Recipients must then comply with the ARs listed in the NOFO. Do not include any ARs that do not apply to this NOFO. NOFO Recipients must comply with administrative and national policy requirements as appropriate. For more information on the Code of Federal Regulations, visit the National Archives and Records Administration: <http://www.access.gpo.gov/nara/cfr/cfr-table-search.html>.

Specific requirements that apply to this NOFO are the following:

Generally applicable ARs:

[AR-1: Human Subjects Requirements](#)

[AR-2: Requirements for Inclusion of Women and Racial and Ethnic Minorities in Research](#)

[AR-9: Paperwork Reduction Act Requirements](#)

[AR-10: Smoke-Free Workplace Requirements](#)

[AR-11: Healthy People 2020](#)

[AR-12: Lobbying Restrictions](#)

[AR-13: Prohibition on Use of CDC Funds for Certain Gun Control Activities](#)

[AR-14: Accounting System Requirements](#)

[AR-21: Small, Minority, And Women-owned Business](#)

[AR-22: Research Integrity](#)

[AR-24: Health Insurance Portability and Accountability Act Requirements](#)

[AR-25: Data Management and Access](#)

[AR-26: National Historic Preservation Act of 1966](#)

[AR-28: Inclusion of Persons Under the Age of 21 in Research](#)

[AR-29: Compliance with EO13513, "Federal Leadership on Reducing Text Messaging while Driving", October 1, 2009](#)

[AR-30: Information Letter 10-006, - Compliance with Section 508 of the Rehabilitation Act of](#)

[1973](#)

[AR-31: Research Definition](#)

[AR-32: Appropriations Act, General Provisions](#)

[AR-33: United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern](#)

[AR-34: Language Access for Persons with Limited English Proficiency](#)

Organization Specific ARs:

[AR-8: Public Health System Reporting Requirements](#)

[AR-15: Proof of Non-profit Status](#)

[AR 23: Compliance with 45 C.F.R. Part 87](#)

3. Additional Policy Requirements

The following are additional policy requirements relevant to this NOFO:

HHS Policy on Promoting Efficient Spending: Use of Appropriated Funds for Conferences and Meetings, Food, Promotional Items and Printing Publications This policy supports the Executive Order on Promoting Efficient Spending (EO 13589), the Executive Order on Delivering and Efficient, Effective, and Accountable Government (EO 13576) and the Office of Management and Budget Memorandum on Eliminating Excess Conference Spending and Promoting Efficiency in Government (M-35-11). This policy apply to all new obligations and all funds appropriated by Congress. For more information, visit the HHS website at: <https://www.hhs.gov/grants/contracts/contract-policies-regulations/efficient-spending/index.html>.

Federal Funding Accountability and Transparency Act of 2006 Federal Funding Accountability and Transparency Act of 2006 (FFATA), P.L. 109–282, as amended by section 6202 of P.L. 110–252, requires full disclosure of all entities and organizations receiving Federal funds including grants, contracts, loans and other assistance and payments through a single, publicly accessible website, www.usaspending.gov. For the full text of the requirements, please review the following website: <https://www.fsrc.gov/>.

Plain Writing Act The Plain Writing Act of 2010, Public Law 111-274 was signed into law on October 13, 2010. The law requires that federal agencies use "clear Government communication that the public can understand and use" and requires the federal government to write all new publications, forms, and publicly distributed documents in a "clear, concise, well-organized" manner. For more information on this law, go to: <http://www.plainlanguage.gov/plLaw/index.cfm>.

Pilot Program for Enhancement of Employee Whistleblower Protections All applicants will be subject to a term and condition that applies the terms of 48 CFR section 3.908 to the award

and requires that recipients inform their employees in writing (in the predominant native language of the workforce) of employee whistleblower rights and protections under 41 U.S.C. 4712.

Copyright Interests Provision This provision is intended to ensure that the public has access to the results and accomplishments of public health activities funded by CDC. Pursuant to applicable grant regulations and CDC's Public Access Policy, Recipient agrees to submit into the National Institutes of Health (NIH) Manuscript Submission (NIHMS) system an electronic version of the final, peer-reviewed manuscript of any such work developed under this award upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. Also at the time of submission, Recipient and/or the Recipient's submitting author must specify the date the final manuscript will be publicly accessible through PubMed Central (PMC). Recipient and/or Recipient's submitting author must also post the manuscript through PMC within twelve (12) months of the publisher's official date of final publication; however the author is strongly encouraged to make the subject manuscript available as soon as possible. The recipient must obtain prior approval from the CDC for any exception to this provision.

The author's final, peer-reviewed manuscript is defined as the final version accepted for journal publication, and includes all modifications from the publishing peer review process, and all graphics and supplemental material associated with the article. Recipient and its submitting authors working under this award are responsible for ensuring that any publishing or copyright agreements concerning submitted articles reserve adequate right to fully comply with this provision and the license reserved by CDC. The manuscript will be hosted in both PMC and the CDC Stacks institutional repository system. In progress reports for this award, recipient must identify publications subject to the CDC Public Access Policy by using the applicable NIHMS identification number for up to three (3) months after the publication date and the PubMed Central identification number (PMCID) thereafter.

Language Access for Persons with Limited English Proficiency Recipients of federal financial assistance from HHS must administer their programs in compliance with federal civil rights law. This means that recipients of HHS funds must ensure equal access to their programs without regard to a person's race, color, national origin, disability, age and, in some circumstances, sex and religion. This includes ensuring your programs are accessible to persons with limited English proficiency. Recipients of federal financial assistance must take the reasonable steps to provide meaningful access to their programs by persons with limited English proficiency.

Dual Use Research of Concern On September 24, 2014, the US Government Policy for the Institutional Oversight of Life Sciences Dual Use Research of Concern was released. Recipients (foreign and domestic) receiving CDC funding on or after September 24, 2015 are subject to this policy. Research funded by CDC involving the agents or toxins named in the policy, must be reviewed to determine if it involves one or more of the listed experimental effects and if so, whether it meets the definition of DURC. This review must be completed by an Institutional Review Entity (IRE) identified by the funded institution.

Recipients also must establish an Institutional Contact for Dual Use Research (ICDUR). The award recipient must maintain records of institutional DURC reviews and completed risk mitigation plans for the term of the research grant, cooperative agreement or contract plus three years after its completion, but no less than eight years, unless a shorter period is required by law

or regulation.

If a project is determined to be DURC, a risk/benefit analysis must be completed. CDC will work collaboratively with the award recipient to develop a risk mitigation plan that the CDC must approve. The USG policy can be found at <http://www.phe.gov/s3/dualuse>.

Non-compliance with this Policy may result in suspension, limitation, restriction or termination of USG funding, or loss of future USG funding opportunities for the non-compliant USG-funded research project and of USG funds for other life sciences research at the institution, consistent with existing regulations and policies governing USG funded research, and may subject the institution to other potential penalties under applicable laws and regulations.

Data Management Plan(s)

CDC requires that all new collections of public health data include a Data Management Plan (DMP). For purposes of this announcement, “public health data” means digitally recorded factual material commonly accepted in the scientific community as a basis for public health findings, conclusions, and implementation.

This new requirement ensures that CDC is in compliance with the following; Office of Management and Budget (OMB) memorandum titled “Open Data Policy–Managing Information as an Asset” (OMB M-13-13); Executive Order 13642 titled “Making Open and Machine Readable the New Default for Government Information”; and the Office of Science and Technology Policy (OSTP) memorandum titled “Increasing Access to the Results of Federally Funded Scientific Research” (OSTP Memo).

The AR-25 <https://www.cdc.gov/grants/additionalrequirements/ar-25.html> outlines the components of a DMP and provides additional information for investigators regarding the requirements for data accessibility, storage, and preservation.

4. Cooperative Agreement Terms and Conditions

The PD(s)/PI(s) will have the primary responsibility for:

- Complying with the responsibilities for the Extramural Investigators as described in the Policy on Public Health Research and Nonresearch Data Management and Access
- Participate in the CBDRP Coordinating Council
- Ensuring that all staff members are aware of the responsibilities associated with using data from NBDPS and BD-STEPS, and follow the datasharing guidelines
- Will develop the research protocol and submit the protocol for human subjects review and for OMB clearance as required (OMB/PRA requirements are expected to apply.)
- To the extent applicable, maintaining data consistent with Section 301(d) of the Public Health Service Act, 42 U.S.C. 241(d), as amended.

Recipients will retain custody of and have primary rights to the data and software developed under these awards, subject to Government rights of access consistent with current DHHS, PHS, and CDC policies.

In this cooperative agreement, a NCBDDD Scientific Collaborator (SC) is a partner with scientific and programmatic involvement during the conduct of the project through technical assistance, advice, and coordination. For both Component A. BD-STEPS II Core and Component

B. BD-STEPS stillbirth, the SC will:

- Use their experience in studies of this nature to advise the project on specific questions regarding the project.
- Provide scientific consultation and technical assistance in the development, implementation, and conduct of the evaluation study.
- Assist in the development of the research protocol for Institutional Review Board (IRB) review and other required reviews and approvals.
- OMB/PRA requirements are expected to apply and CDC will work with awardee to obtain OMB approvals as required.
- Obtain a Certificate of Confidentiality to protect participating subjects, particularly given the sensitivity of genetic data that will be collected.
- Obtain IRB approvals as required by CDC if CDC is engaged in research involving human subjects.
- Provide assistance on and participate in data analysis, interpretation, and reporting of findings in the literature.
- Participate in monthly, or more frequent, conference calls with recipient.

CDC staff have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below:

Component A. BD-STEPS II Core

- Specifically, for this program, CDC will collaborate as a full center, providing cases and controls from Metropolitan Atlanta to the centralized tracking database and clinical database.
- Participate in all committees and work groups.
- Analyze data and prepare manuscripts.
- CDC will also provide technical assistance on clinical, epidemiological, and biological questions for BD-STEPS.
- For data management, CDC will develop a data management plan for the study to include databases for the clinical, interview, and biologics data.
- Provide technical assistance and guidance on analysis, interpretation, and reporting of findings in the literature that can serve a broad range of scientific interests.
- Serve on the Coordinating Council.
- Obtain and maintain the central CDC IRB approval, obtain and maintain OMB approval for the study, and maintain the Certificate of Confidentiality.
- Participate in designing, developing, and evaluating methodologies and approaches used for population-based birth defects surveillance and research.
- Participate in the collection, management, and analysis of data related to birth defects.
- Provide training and quality control exercises for use of the data from NBDPS and BD-STEPS, as well as guidance for potentially combining data from the two studies.
- For those laboratories that will be analyzing the DNA samples, CDC will coordinate the quality assurance/quality control exercises.
- Participate in the development, implementation, and conduct of the study protocol.
- Participate in the sharing of information between the participating CDRPs (e.g. data

- sharing document formats, clinical, and biologic databases, potential research issues, etc.).
- Serve as a resource for sharing state, regional and national data and information pertinent to the surveillance, research, and prevention of birth defects.
- Manage the following activities: central lab and centralized biorepository; shared databases (tracking, analysis, biologic, data sharing); and centralized interviewing and provide any needed software applications.

Component B. BD-STEPS stillbirth

- CDC will provide technical assistance on clinical, epidemiological, and biological questions for stillbirth research and BD-STEPS.
- For data management, CDC will develop a data management plan for the study to include databases for the clinical, interview, and biologics data.
- Provide technical assistance and guidance on analysis, interpretation, and reporting of findings in the literature that can serve a broad range of scientific interests.
- Obtain and maintain the central CDC IRB approval, obtain and maintain OMB approval for the study, and maintain the Certificate of Confidentiality.
- Participate in designing, developing, and evaluating methodologies and approaches used for population-based birth defects surveillance and research.
- Participate in the development, implementation, and conduct of the study protocol.
- Participate in the sharing of information between the participating CDRPs (e.g. data sharing document formats, clinical databases, potential research issues, etc.).
- Serve as a resource for sharing state, regional and national data and information pertinent to the surveillance, research, and prevention of birth defects.
- Manage the following activities: shared databases (tracking, analysis, biologic, data sharing); and centralized interviewing and provide any needed software applications.

Additionally, an HHS/CDC Project Officer or other HHS/CDC staff will provide day-to-day programmatic, administrative, and fiscal management in support of the project as defined above.

Additionally, an HHS/CDC agency Scientific Program Official (SPO) will be responsible for the normal scientific and programmatic stewardship of the award. For Component A. BD-STEPS II Core and Component B. BD-STEPS stillbirth, The SPO will be:

- Named in the Notice of Grant Award (NGA) as the Program Official to provide oversight and assure overall scientific and programmatic stewardship of the award;
- Monitor performance against approved project objectives; and
- Assure assessment of the public health impact of the research conducted under this Notice Of Funding Opportunity and promote translation of promising practices, programs, interventions, and other results from the research.

Areas of Joint Responsibility include:

- Finalizing the protocol and interview instrument.
- Membership of data sharing committee, clinician committee, and coordinating council.
- Participate fully in conference calls and other communication between CDC and other recipients.

- Funded institutions will use all of the agreed-upon methods and protocols including the clinical, tracking, biologic, and other database formats to input, maintain, and backup all data
- Use generally accepted epidemiological methods to evaluate results.
- Publish the results in peer-reviewed journals.

5. Reporting

Recipients will be required to complete Research Performance Progress Report (RPPR) in eRA Commons at least annually (see <https://grants.nih.gov/grants/rppr/index.htm>; https://grants.nih.gov/grants/forms/report_on_grant.htm) and financial statements as required in the HHS Grants Policy Statement.

A final progress report, invention statement, equipment inventory list and the expenditure data portion of the Federal Financial Report are required for closeout of an award, as described in the HHS Grants Policy Statement.

Although the financial plans of the HHS/CDC CIO(s) provide support for this program, awards pursuant to this funding opportunity depend upon the availability of funds, evidence of satisfactory progress by the recipient (as documented in required reports) and the determination that continued funding is in the best interest of the Federal government.

The **Federal Funding Accountability and Transparency Act of 2006 (Transparency Act)**, includes a requirement for recipients of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later.

Compliance with this law is primarily the responsibility of the Federal agency. However, two elements of the law require information to be collected and reported by recipients:

1) **Information on executive compensation when not already reported through the SAM Registration; and**

2) **Similar information on all sub-awards/ subcontracts/ consortiums over \$25,000.** It is a requirement for recipients of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later.

All recipients of applicable CDC grants and cooperative agreements are required to report to the Federal Subaward Reporting System (FSRS) available at www.fsrs.gov on all subawards over \$25,000. See the HHS Grants Policy

Statement (<https://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf>).

A. Submission of Reports

The Recipient Organization must provide HHS/CDC with an original, plus one hard copy of the following reports:

1. **Yearly Non-Competing Grant Progress Report** is due 90 to 120 days before the end of the current budget period. The RPPR form (<https://grants.nih.gov/grants/rppr/index.htm>; https://grants.nih.gov/grants/rppr/rppr_instruction_guide.pdf) is to be completed on the eRA Commons website. The progress report will serve as the non-competing

continuation application. Although the financial plans of the HHS/CDC CIO(s) provide support for this program, awards pursuant to this funding opportunity are contingent upon the availability of funds, evidence of satisfactory progress by the recipient (as documented in required reports) and the determination that continued funding is in the best interest of the Federal government.

2. **Annual Federal Financial Report (FFR) SF 425**
https://grants.nih.gov/grants/forms/report_on_grant/federal_financial_report_ffr.htm
required and must be submitted through eRA Commons **within 90 days after the end of the calendar quarter in which the budget period ends.**
3. **A final progress report**, invention statement, equipment/inventory report, and the final FFR are required **90 days after the end of the Period of Performance.**

B. Content of Reports

1. Yearly Non-Competing Grant Progress Report: The recipient's continuation application/progress should include

- Description of Progress during Annual Budget Period: Current Budget Period Progress reported on the RPPR form in eRA Commons (<https://grants.nih.gov/grants/rppr/index.htm>). Detailed narrative report for the current budget period that directly addresses progress towards the Measures of Effectiveness included in the current budget period proposal.
- Research Aims: list each research aim/project
 - a) Research Aim/Project: purpose, status (met, ongoing, and unmet), challenges, successes, and lessons learned
 - b) Leadership/Partnership: list project collaborations and describe the role of external partners.
- Translation of Research (1 page maximum). When relevant to the goals of the research project, the PI should describe how the significant findings may be used to promote, enhance, or advance translation of the research into practice or may be used to inform public health policy. This section should be understandable to a variety of audiences, including policy makers, practitioners, public health programs, healthcare institutions, professional organizations, community groups, researchers, and other potential users. The PI should identify the research findings that were translated into public health policy or practice and how the findings have been or may be adopted in public health settings. Or, if they cannot be applied yet, this section should address which research findings may be translated, how these findings can guide future research or related activities, and recommendations for translation. If relevant, describe how the results of this project could be generalized to populations and communities outside of the study. *Questions to consider in preparing this section include:*

- How will the scientific findings be translated into public health practice or inform public health policy?
- How will the project improve or effect the translation of research findings into public health practice or inform policy?
- How will the research findings help promote or accelerate the dissemination, implementation, or diffusion of improvements in public health programs or practices?
- How will the findings advance or guide future research efforts or related activities?
- Public Health Relevance and Impact (1 page maximum). This section should address improvements in public health as measured by documented or anticipated outcomes from the project. The PI should consider how the findings of the project relate beyond the immediate study to improved practices, prevention or intervention techniques, inform policy, or use of technology in public health. *Questions to consider in preparing this section include:*
 - How will this project lead to improvements in public health?
 - How will the findings, results, or recommendations been used to influence practices, procedures, methodologies, etc.?
 - How will the findings, results, or recommendations contributed to documented or projected reductions in morbidity, mortality, injury, disability, or disease?
- Current Budget Period Financial Progress: Status of obligation of current budget period funds and an estimate of unobligated funds projected provided on an estimated FFR.
- New Budget Period Proposal:
 - Detailed operational plan for continuing activities in the upcoming budget period, including updated Measures of Effectiveness for evaluating progress during the upcoming budget period. Report listed by Research Aim/Project.
 - Project Timeline: Include planned milestones for the upcoming year (be specific and provide deadlines).
- New Budget Period Budget: Detailed line-item budget and budget justification for the new budget period. Use the CDC budget guideline format.
- Publications/Presentations: Include publications/presentations resulting from this CDC grant only during this budget period. If no publication or presentations have been made at this stage in the project, simply indicate "Not applicable: No publications or presentations have been made."
- IRB Approval Certification: Include all current IRB approvals to avoid a funding restriction on your award. If the research does not involve human subjects, then please state so. Please provide a copy of the most recent local IRB and CDC IRB, if applicable. If any approval is still pending at time of APR due date, indicate the status in your narrative.

- **Update of Data Management Plan:** The DMP is considered a living document that will require updates throughout the lifecycle of the project. Investigators should include any updates to the project's data collection such as changes to initial data collection plan, challenges with data collection, and recent data collected. Applicants should update their DMP to reflect progress or issues with planned data collection and submit as required for each reporting period.
- **Additional Reporting Requirements:**

Not Applicable.

2. Annual Federal Financial Reporting The Annual Federal Financial Report (FFR) SF 425 is required and must be submitted through eRA Commons within 90 days after the end of the calendar quarter in which the budget period ends. The FFR should only include those funds authorized and disbursed during the timeframe covered by the report. The final FFR must indicate the exact balance of unobligated funds and may not reflect any unliquidated obligations. There must be no discrepancies between the final FFR expenditure data and the Payment Management System's (PMS) cash transaction data.

Failure to submit the required information in a timely manner may adversely affect the future funding of this project. If the information cannot be provided by the due date, you are required to submit a letter explaining the reason and date by which the Grants Officer will receive the information.

The due date for final FFRs will continue to be 90 days after the Period of Performance end date. Recipients must submit closeout reports in a timely manner. Unless the Grants Management Officer (GMO) of the awarding Institute or Center approves an extension, recipients must submit a final FFR, final progress report, and Final Invention Statement and Certification within 90 days of the end of grant period. Failure to submit timely and accurate final reports may affect future funding to the organization or awards under the direction of the same Project Director/Principal Investigator (PD/PI).

FFR (SF 425) instructions for CDC recipients are now available at https://grants.nih.gov/grants/forms/report_on_grant/federal_financial_report_ffr.htm. For further information, contact GrantsInfo@nih.gov. Additional resources concerning the eFSR/FFR system, including a User Guide and an on-line demonstration, can be found on the eRA Commons Support Page: <https://grants.nih.gov/support/index.html>

FFR Submission: The submission of FFRs to CDC will require organizations to register with eRA Commons (Commons) (<https://commons.era.nih.gov/commons/>). CDC recommends that this one time registration process be completed at least 2 weeks prior to the submittal date of a FFR submission.

Organizations may verify their current registration status by running the "List of Commons Registered Organizations" query found at: https://era.nih.gov/registration_accounts.cfm.

Organizations not yet registered can go to <https://commons.era.nih.gov/commons/> for instructions. It generally takes several days to complete this registration process. This registration

is independent of Grants.gov and may be done at any time.

The individual designated as the PI on the application must also be registered in the Commons. The PI must hold a PI account and be affiliated with the applicant organization. This registration must be done by an organizational official or their delegate who is already registered in the Commons. To register PIs in the Commons, refer to the eRA Commons User Guide found at: https://era.nih.gov/docs/Commons_UserGuide.pdf.

3. Final Reports: Final reports should provide sufficient detail for CDC to determine if the stated outcomes for the funded research have been achieved and if the research findings resulted in public health impact based on the investment. The recipient's final report should include:

- **Research Aim/Project Overview:** The PI should describe the purpose and approach to the project, including the outcomes, methodology and related analyses. Include a discussion of the challenges, successes and lessons learned. Describe the collaborations/partnerships and the role of each external partner.
- **Translation of Research Findings:** The PI should describe how the findings will be translated and how they will be used to inform policy or promote, enhance or advance the impact on public health practice. This section should be understandable to a variety of audiences, including policy makers, practitioners, public health programs, healthcare institutions, professional organizations, community groups, researchers and other potential end users. The PI should also provide a discussion of any research findings that informed policy or practice during the course of the Period of Performance. If applicable, describe how the findings could be generalized and scaled to populations and communities outside of the funded project.
- **Public Health Relevance and Impact:** This section should address improvements in public health as measured by documented or anticipated outcomes from the project. The PI should consider how the findings of the project related beyond the immediate study to improved practices, prevention or intervention techniques, or informed policy, technology or systems improvements in public health.
- **Publications; Presentations; Media Coverage:** Include information regarding all publications, presentations or media coverage resulting from this CDC funded activity. Please include any additional dissemination efforts that did or will result from the project.
- **Final Data Management Plan:** Applicants must include an updated final Data Management Plan that describes the data collected, the location of where the data is stored (example: a repository), accessibility restrictions (if applicable), and the plans for long term preservation of the data.

Section VII. Agency Contacts

We encourage inquiries concerning this funding opportunity and welcome the opportunity to

answer questions from potential applicants.

Application Submission Contacts

[Grants.gov Customer Support](#) (Questions regarding Grants.gov registration and submission, downloading or navigating forms)

Contact Center Phone: 800-518-4726

Email: support@grants.gov

Hours: 24 hours a day, 7 days a week; closed on Federal holidays

[eRA Commons Help Desk](#) (Questions regarding eRA Commons registration, tracking application status, post submission issues, FFR submission)

Phone: 301-402-7469 or 866-504-9552 (Toll Free)

TTY: 301-451-5939

Email: commons@od.nih.gov

Hours: Monday - Friday, 7am - 8pm U.S. Eastern Time

CDC Technical Information Management Section (TIMS)

Telephone 770-488-2700

Email: ogstims@cdc.gov

Hours: Monday - Friday, 7am – 4:30pm U.S. Eastern Time

Scientific/Research Contact(s)

Marcella Law

Scientific Program Official

Extramural Research Program Operations and Services

Centers for Disease Control and Prevention (CDC)

4770 Buford Highway, NE

Mailstop F-80

Atlanta, GA 30342

Telephone: (770)-488-5416

Email: mah7@cdc.gov

Peer Review Contact(s)

Jaya Raman, Ph.D

Scientific Review Official

Extramural Research Program Operations and Services

CDC

4770 Buford Highway, NE

Mailstop F-80

Atlanta, GA 30342

Telephone: (770)-488-6511

Email: kva@cdc.gov

Financial/Grants Management Contact(s)

LaKasa Wyatt

Grants Management Specialist (GMS), Office of Financial Resources, Office of Grants Services
CDC

2920 Brandywine Road, M/S E-09, Atlanta, GA 30341

Telephone: 770-488-2728 Email: lgw5@cdc.gov

Section VIII. Other Information

Other CDC Notices of Funding Opportunities can be found at www.grants.gov.

All awards are subject to the terms and conditions, cost principles, and other considerations described in the HHS Grants Policy Statement.

Authority and Regulations

Awards are made under the authorization of Sections of the Public Health Service Act as amended and under the Code Federal Regulations.

This program is authorized under Sections 301 and 317C of the Public Health Service Act [42 U.S.C. 241, and 247b-4 as amended].

APPENDIX A: Potential Applicant Questions and CDC Response

Q1: On page 22 & 23 of the above RFA there is an indication to use the SF424 R&R instructions unless the NOFO indicates otherwise. I'm a bit confused as to whether or not we are to include an introduction on the PHS398 Research Plan. The introduction, per the SF 424 R&R instructions is only included for resubmissions and revision application and the content is supposed to be a descriptive of changes in the application. The instructions in this RFA indicate "provide a clear description about the purpose of the research and how it addresses the specific requirements of the NOFO". This leads me to believe you wish for this letter to be included. We are happy to provide the introduction letter, however this application will fail validation in eRA commons if an introduction letter is included when it is not a resubmission or revision application (this information is noted on the SF 424 cover page).

A1: An introduction letter is not required for a new application.

Q2: The NOFO instructions state that we may contact you to **obtain the “draft Protocol”** (e.g., the NOFO refers to the draft Protocol on p. 10 Data and Specimen Collection and p. 13 Data Reporting). In addition, **would you please send me the overall BD-STEPS II draft protocol**

and any other related protocols available for this NOFO? We will need protocol details to develop proposal plans and proposed budget for the local BD-STEPS II ascertainment, data collection and mailings activities.

A2: We are attaching 4 pdf files of the current BD-STEPS and Stillbirths protocols and questionnaires.

Q3: We are reviewing the NOFO for BD-STEPS II (RFA-DD-18-001) and would like to request some additional documentation: (a) The RFA states on page 10 that “recipients are expected to conduct a pilot project to validate maternal self-reported medication use during pregnancy”; and (b) Similarly, on pages 12-13, a draft protocol for the stillbirth study/Component B is referenced as available upon request.

A3a: There is not an existing protocol for the pilot project to validate maternal self-reported medication use during pregnancy. Applicants are expected to propose a project design and conduct the pilot project as part of their application. The announcement includes suggestions for possible data sources for the pilot project, but other data sources may also be used.

A3b: We are attaching 4 pdf files of the current BD-STEPS and Stillbirths protocols and questionnaires.

Q4: The award ceiling for Component A: BD-STEPS II Core is listed as \$1,000,000 and for Component B: BD-STEPS Stillbirth is listed as \$250,000; however, the overall award ceiling amount is \$1,100,000. We interpret this to mean we cannot apply for the award ceiling for both components, as it would add up to more than the \$1,100,000, is that correct?

A4: Incorrect, you can submit an application up to \$1,000,000 for Component A and an application up to \$250,000 for Component B. The total of both applications would be \$1,250,000. The amount of \$1,100,000 is our estimated actual average funding amount per year comprised of \$900,000 for Component A and \$200,000 for Component B.

Q5: In the instructions it specifies a planned enrollment table, is there a template for this item? We have not found a template in the forms section in grants.gov.

A5: The PHS 398 Grant Application form includes a blank template entitled “PHS Inclusion Enrollment Report (OMB Number: 0925-0001 and 0925-0002).”

Q6: Does a pediatric cardiologist have to classify the heart defects? If so, can you clarify how you are defining a pediatric cardiologist? (Is it someone who has been trained in this specialty? Someone who is board certified in this specialty? Someone who actively practices in this specialty?)

A6: Yes, all cardiac cases will be divided among the pediatric cardiologists available from across all awardees and the CDC program office for review and classification. In this NOFO, a pediatric cardiologist is defined as someone who has a medical doctoral degree

(MD or DO) with prior experience or expertise in the field of pediatric cardiology. A clinical geneticist at each awardee must review all cases from that respective awardee for eligibility to be included in the study.

Q7: The NOFO asks about collaborative projects with other birth defects surveillance systems since 1/1/2010. Is this question focused on state surveillance systems or can it also be interpreted to include collaboration with other types of surveillance systems (e.g. hospital-based or case-control studies other than BD-STEPS/NBDPS)?

A7: Applicants may provide descriptions of any collaborative projects they feel incorporates some form of birth defects surveillance data. However, BD-STEPS includes only data from active, population-based surveillance systems. Demonstration of previous collaborations with active, population-based surveillance systems are most relevant to the current NOFO. In addition, previous collaboration with the surveillance system that will be the source for cases for the applicant should be a focus of this description. The NOFO will be amended to clarify this topic.

Q8: We would also like to have a copy of the most recent version of the main BD-STEPS questionnaire (Component A), which may be a separate document.

A8: We are attaching 4 pdf files of the current BD-STEPS and Stillbirths protocols and questionnaires.

Q9: Is it correct to assume that the scientific review will be conducted by a Special Emphasis Panel, comprised of reviewers external to CDC?

A9: As stated in the NOFO, applications will be evaluated for scientific and technical merit by an appropriate peer review group, in accordance with CDC peer review policy and procedures, using the stated review criteria. This includes review by an external review panel.

Q10: Please send a list of the BPA/CDC codes that define the desired phenotypes.

A10: We are attaching a pdf file of the included BPA/CDC codes that have already been established. For some defects, a final decision on which BPA/CDC codes to include will be made in collaboration with the awardees.

Q11: Pertaining to the birth defects listed in Table 1, (a) do we have to currently track all the birth defects listed in Table 1 to be eligible to submit an application? (b) Do you have any specific birth defects for posterior eye defects which appears to be very broad? (c) Does anomalous pulmonary venous return stand for “total” anomalous pulmonary venous return only or “partial” too?

A11a: The NOFO does not require applicants to currently track all the birth defects listed in Table 1 to be eligible to apply. Eligibility requirements are listed in Section III.

Eligibility Information. If applicants do not currently track all of the birth defects listed in Table 1, they should describe as part of their application how they will incorporate case finding for these defects into their surveillance system. The NOFO will be amended to clarify this topic.

A11b: We are attaching a pdf file of the included BPA/CDC codes that have already been established.

A11c: In Table 1, only total anomalous pulmonary venous return is included.

Q12: Please provide a copy of the draft protocol for validating maternal self-reported medication use during pregnancy.

A12: There is not an existing protocol for the pilot project to validate maternal self-reported medication use during pregnancy. Applicants are expected to propose a project design as part of their application. The announcement includes suggestions for possible data sources for the pilot project, but other data sources may also be used.

Q13: NOFO #RFA-DD18-001, page 18, requires “A list or table of counties with number of annual births for **2015** with race/ethnicity that confirm 30,000-75,000 births annually in the selected geographic area” whereas page 26 instructions (b) instruct us to “Describe your study catchment area and the corresponding birth population size in the area in **2016** (must include 30,000 – 75,000 births annually).” **Please let us know whether to present information for 2015 or 2016.**

A13: Numbers from either 2015 or 2016 may be provided. The NOFO will be amended to indicate that either year may be submitted.

Q14: Will the list of external reviewers be released prior to submission or is there a link where we can view them?

A14: A list of the external reviewers will not be released prior to the application due date. After the review, each applicant will receive a list of the panel members who reviewed the applications.

Q15: By what date will we be notified of funding decisions?

A15: We anticipate late July 2018.

Q16: What defects are included in the “cataracts/glaucoma” category and the “posterior eye defect” category?

A16: We are attaching a pdf file of the included BPA/CDC codes that have already been established. For some defects, a final decision on which BPA/CDC codes to include will be made in collaboration with the awardees.

Q17: It would be helpful to receive a listing of the ICD and/or BPA codes for the birth defects listed in Table 1.

A17: We are attaching a pdf file of the included BPA/CDC codes that have already been established. For some defects, a final decision on which BPA/CDC codes to include will be made in collaboration with the awardees.

Q18: Table 1 questions: (a) For “anomalous pulmonary venous return” – restrict to **total** anomalous pulmonary venous return (TAPVR)? (we currently collect only TAPVR for BD-STEPS and do not include partial anomalous pulmonary venous return); and (b) For “cataracts, glaucoma,” we will plan to list cataracts and glaucoma prevalences separately unless you advise otherwise.

A18: BD-STEPS II will also be limited to TAPVR, just like BD-STEPS I. We are attaching a pdf file of the included BPA/CDC codes that have already been established. For some defects, a final decision on which BPA/CDC codes to include will be made in collaboration with the awardees.

Q19: Would CDC like us to exclude cases with co-occurring chromosomal or syndromic birth defects?

A19: Yes, as clarified in the attached pdf file of specific birth defect descriptions: “In general, fetuses/infants with chromosomal/microdeletion disorders or single gene disorders are excluded”.

Q20: Since it says “draft” protocol, does this refer to a draft protocol for BD-STEPS II or does this refer to the current BD-STEPS protocol? If there is a draft BD-STEPS II protocol, I would like to receive it since it might contain details on the consenting process for access to NEDSS data (verbal/written, before interview/after, etc.).

A20: We are attaching 4 pdf files of the current BD-STEPS and Stillbirths protocols and questionnaires. Additionally, we are attaching a pdf file of the included BPA/CDC codes that have already been established. For some defects, a final decision on which BPA/CDC codes to include will be made in collaboration with the awardees.