

Centers for Disease Control and Prevention

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

Public Health Research on Modifiable Risk Factors for Spina Bifida
RFA-DD-15-001
Application Due Date: 02/24/2015

Public Health Research on Modifiable Risk Factors for Spina Bifida

RFA-DD-15-001

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Part 1. Overview Information

Participating Organization(s)

Centers for Disease Control and Prevention

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)

Funding Opportunity Announcement (FOA) Title

Public Health Research on Modifiable Risk Factors for Spina Bifida

Activity Code

AMENDMENT 1 made on February 3, 2015.

- **Appendix A "Questions from Potential Applicants and CDC Responses" added to Section VIII. Other Information.**
- **Attachment 1 "Selected Public Health Priorities for the Identification and Confirmation of Spina Bifida Risk Factors Based on Recent CDC-Funded Studies" added to Section VIII. Other Information.**

U01

Funding Opportunity Announcement Type

New

Funding Opportunity Announcement Number

RFA-DD-15-001

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

93.073

Category of Funding Activity:

Health

FOA Purpose

This FOA solicits applications in the form of cooperative agreements to investigate potentially modifiable risk factors for spina bifida in the presence of adequate folate (i.e. where there is established mandatory folic acid fortification or among populations for which there is individual-level data on periconceptional folic acid use), including identification of novel risk factors, identification of factors that may alter the impact of established risk factors (e.g. physical activity and obesity), and replication of previously observed associations from population-based epidemiological studies (e.g. National Birth Defects Prevention Study).

Key Dates

Publication Date:	**To receive notification of any changes to RFA-DD-15-001, 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 needed for this service.**
Letter of Intent Due Date:	**01/23/2015**
Application Due Date:	**02/24/2015**

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: **04/01/2015**

Secondary Review: **06/01/2015**

Estimated Start Date: **09/01/2015**

Expiration Date: **02/21/2015**

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 FOA. Conformance to all requirements (both in the Application Guide and the FOA) 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.** This FOA solicits applications in the form of cooperative agreements to investigate potentially modifiable risk factors for spina bifida in the presence of adequate folate (i.e. where there is established mandatory folic acid fortification or among populations for which there is individual-level data on periconceptional folic acid use), including identification of novel risk factors, identification of factors that may alter the impact of established risk factors (e.g. physical activity and obesity), and replication of previously observed associations from population-based epidemiological studies (e.g. National Birth Defects Prevention Study).
- **Mechanism of Support.** Cooperative agreement
- **Funds Available and Anticipated Number of Awards.** We anticipate up to 2 awards being made under this FOA and total available funding of approximately $1,800,000 over the entire project period. Awards issued under this FOA are contingent upon availability 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.** The estimated total funding (direct and indirect) for the first year (12 month budget period) is $600,000 ($300,000 per applicant with up to 2 applicants awarded) and the estimated total funding (direct and indirect) for the entire project period is $1,800,000. The budget period is anticipated to be 09/01/2015 to 08/31/2016 and the estimated project period will run from 09/01/2015 to 08/31/2018.
- **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. Institutions that are funded under FOA #DD13-003(Birth Defects Study to Evaluate Pregnancy exposureS, BD-STEPS) may not propose analysis of NBDPS data under this FOA #DD15-001 due to funding overlap.
- **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 contain more than one PI; however, the first PI listed will be the "contact PI" for all correspondence.
- **Number of Applications.** Eligible applicant institutions may submit no more than one application.
- **Application Type.** New
- **Special Date(s).** Not applicable
- **Application Materials.** See Section IV.1 for application materials.
- **Hearing Impaired.** Telecommunications for the hearing impaired are available at: TTY: (770) 488-2783.

Part 2. Full Text

Section I. Funding Opportunity Description

Statutory Authority

Section 301 and 317C of the Public Health Service Act [42 U.S.C. 241, and 247b-4 as amended].

1. Background and Purpose

Spina bifida is a condition that affects the spine and is usually apparent at birth. It is a type of neural tube defect (NTD). Although the prevalence of spina bifida has declined significantly in the United States since the implementation of mandatory fortification of enriched cereal grain products with folic acid (from 6.4 to 4.1 per 10,000 live births)[1], spina bifida still affects almost 1,500 pregnancies in the United States annually.[2] Worldwide, the March of Dimes estimates that there are over 200,000 spina bifida-affected pregnancies.[2, 3] Children born with spina bifida are at increased risk for infant mortality; although improved medical treatment has improved survival in some areas, those affected by spina bifida are at high risk for severe, lifelong disabilities, including paralysis, hydrocephalus, tethered cord, and neurological deficits.[4]

Both folic acid research and the development and implementation of prevention strategies remain essential components in CDC's public health response to spina bifida. CDC's folic acid research and the development and implementation of strategies to prevent spina bifida build upon other CDC efforts, such as programs that monitor the birth prevalence of spina bifida and other birth defects, an activity critical to monitoring trends and identifying disparities. CDC has identified priority areas for public health research to address current gaps in knowledge for spina bifida. The purpose of this funding announcement is to address some of those gaps by investigating potentially modifiable risk factors for spina bifida in the presence of adequate folate (i.e. where there is established mandatory folic acid fortification or among populations for which there is individual-level data on

periconceptional folic acid use), including identification of novel modifiable risk factors, identification of factors that may alter the impact of established risk factors (e.g. physical activity and obesity), and replication of previously observed associations from population-based studies (e.g. National Birth Defects Prevention Study).

Healthy People 2020 and other National Strategic Priorities

The National Center on Birth Defects and Developmental Disabilities (NCBDDD) of CDC within HHS is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2020". This RFA addresses "Healthy People 2020" priority area of Maternal, Infant, and Child Health, and specifically Objective MICH-28.1, "Reduce the occurrence of spina bifida".

Public Health Impact

Each year spina bifida affects pregnancies of more than a thousand families in the U.S., and hundreds of thousands of families worldwide. Children born with spina bifida are at increased risk of death and disability, including paralysis and neurological deficits, with large lifetime medical costs.There is no known cure for spina bifida, making prevention of this defect of paramount importance.Although periconceptional folic acid use is one proven preventive strategy for spina bifida, not all cases are preventable with sufficient folic acid. Cases continue to occur in the presence of adequate folic acid intake, and therefore other risk factors remain to be identified. The results of this FOAwill aid in the development of new prevention strategies, ultimately allowing women and their healthcare providers to take action toward preventing more cases of spina bifida and maximizing the opportunity for healthy pregnancies and healthy babies.

Relevant Work

Public Health Research on Spina Bifida – A previous cooperative agreement (FOA# DD10-002) between CDC and investigators at Boston University focused on analysis of existing data to examine modifiable risk factors for spina bifida among women who did and did not have the recommended periconceptional folic acid intake for NTD prevention. This project was productive, with research published on a wide variety of topics including: periconceptional opioid analgesic use;[5] periconceptional tea consumption;[6] maternal diabetes and obesity;[7] and maternal periconceptional use of cigarettes, alcohol, and coffee.[8]

National Birth Defects Prevention Study (NBDPS)

The NBDPS is the largest population-based case-control study of birth defects in the U.S. Mothers of more than 30,000 babies with birth defects, including over 2,200 with spina bifida, and 10,000 babies without birth defects took part in the study. Over 150 scientific papers have been published using data from NBDPS including 65 papers that have assessed spina bifida, and although interviewing of mothers for NBDPS stopped in March 2013, analysis of the NBDPS data will continue to identify risk factors for birth defects. Web site: http://www.cdc.gov/ncbddd/birthdefects/nbdps.html.

Birth Defect Study to Evaluate Pregnancy exposureS (BD-STEPS)

BD-STEPS (FOA# DD13-003) builds upon the foundation of birth defects research from NBDPS and further examines findings and follows up on leads from NBDPS research to understand more about what causes birth defects and how to prevent them. BD-STEPS began collecting data on

children born on or after January 1, 2014. Web site: http://www.cdc.gov/ncbddd/birthdefects/bd-steps.html.

Treating for Two Initiative

CDC's Treating for Two: Safer Medication Use in Pregnancy Initiative aims to improve the availability and quality of data to help inform clinical decision-making for women who are pregnant or who could become pregnant. An important part of this initiative is to expand research, including both examination of medications that have not previously been studied for their use during pregnancy, and digging deeper into associations that have been observed, focusing on details of medication-taking such as dose, indication, and concomitant medication use. Web site: http://www.cdc.gov/pregnancy/meds/treatingfortwo/index.html.

This announcement is for research activities supported by CDC. For the definition of research, please see the CDC Web site at the following Internet address: http://www.cdc.gov/od/science/regs/hrpp/researchDefinition.htm

2. Approach

Awardees should utilize pre-existing surveillance data (or population-based registry data) or build on the infrastructure of an existing case-control study to assess risk factors for spina bifida in populations exposed to mandatory folic acid fortification, or populations for which there is complete information available on individual-level use of periconceptional use of folic acid. Awardees should design and conduct an analysis in which a population of pregnancies affected by spina bifida is identified and compared to a reference group of pregnancies not affected by spina bifida. This comparison population must be selected from the same source population as the spina bifida cases. The comparison group should be a representative sample of the source population and not a convenience sample. Inclusion of pregnancies affected by spina bifida that ended in elective termination and stillbirth, in addition to live birth, is strongly encouraged.

Research should focus on 1) identification of novel risk factors; 2) identification of factors that may alter the impact of established risk factors; and/or 3) replication of previously observed associations from population-based epidemiological studies. Research on novel risk factors must focus on potentially modifiable factors which have not previously been assessed for their association with spina bifida, or for which there are few data and/or inconsistent results, but for which biological plausibility for an association exists. Confirmation of well-established risk factors for spina bifida, such as obesity, Hispanic ethnicity, low acculturation, anti-epileptic medication use, and pre-gestational diabetes, is not an acceptable aim of the proposed research. However, a more refined assessment of these risk factors, or other previously reported risk factors, is strongly encouraged. Examples of such investigations include: 1) assessing the potential modifying effect of physical activity on the association between diabetes and/or prepregnancy obesity and spina bifida, and 2) assessing whether specific medications within a medication class (e.g. opioids) or certain doses of medication are more or less associated with spina bifida risk. Associations reported from large, population-based research studies, such as the National Birth Defects Prevention Study (NBDPS), require confirmation from other data sources. NBDPS has reported on many exposures and their association with spina bifida risk, including specific medications and occupational exposures (some selected examples are provided in Attachment 1).

Sites that are receiving funding under FOA #DD13-003 for the Birth Defects Study to Evaluate Pregnancy exposureS (BD-STEPS) are already receiving funding for analyses of

previously-collected NBDPS data and thus may not propose analysis of NBDPS data under this FOA #DD15-001. Sites previously funded for the National Birth Defects Prevention Study (NBDPS) that are not funded under FOA #DD13-003 may propose analyses of NBDPS data under this FOA; however, they must augment this plan by either identifying other sources of data with which to replicate NBDPS findings or justify the importance of using NBDPS data for an original replication of results from other population-based studies of spina bifida risk factors.

While the FOA intent is, among other goals, to develop an assessment of policy interventions designed to reduce the incidence of diabetes, awardees, in providing an assessment, must comply with the provisions in Administrative Requirement 12, Lobbying Restrictions, which prohibits the use of federal funds "related to any activity designed to influence the enactment of legislation, appropriations, regulation, administrative action, or Executive order proposed or pending before the Congress or any state government, state legislature or local legislature or legislative body." More information can be found in Section VI Award Administration Information regarding Administrative Requirement 12.

Objectives/Outcomes

1. Design and develop a plan for analyzing existing data

A research design should be developed that includes a detailed methodology addressing 1) identification of the target population; 2) identification of data source(s); 3) identification of potentially modifiable risk factors and modifying factors of established risk factors to be assessed; and 4) discussion of sample size with power calculations to demonstrate adequate statistical power for the proposed objectives. Analyses should include consideration of demographic factors, such as maternal age, race-ethnicity, education, and family socioeconomic status.

2. Analyze existing data

A plan for analyzing the data from the identified data sources should address the type of data or information to be utilized, and include variables such as: case and control status, including some detailed clinical information; demographic factors, e.g. maternal age, race-ethnicity, education, and family socioeconomic status; maternal health information; pregnancy information, e.g., maternal diet, illnesses and medications used during pregnancy; occupational information; environmental and residential information.

3. Disseminate results of analysis

A plan for disseminating study findings should be developed. The plan should include production and publication of peer-reviewed scientific manuscripts. A confidential abstract draft should be provided to CDC for each manuscript developed that was supported in part or whole by this cooperative agreement; at least 5 published peer-reviewed manuscripts at the end of the 3 year project period on risk factors for spina bifida or other papers furthering the field of spina bifida research are expected.

Target Population

The target population are women with pregnancies affected by spina bifida (cases) and pregnancies not affected by spina bifida (controls) for which information about periconceptional folic acid use can be estimated, either because the population is exposed to mandatory folic acid fortification or from individual-level data on folic acid intake those included in the study.

Collaboration/Partnerships

Collaborations across institutions are encouraged where it can strengthen the ability of the applicant to achieve the purpose of the FOA.

Evaluation/Performance Measurement

The grantees will monitor their progress toward completing their proposed activities.

Translation Plan

It is anticipated that 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. 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. The awardees are expected to produce at least 5 published peer-reviewed manuscripts at the end of the 3 year project period on risk factors for spina bifida or other papers furthering the field of spina bifida research.

References

1. Centers for Disease Control and Prevention, *Spina bifida and anencephaly before and after folic acid mandate--United States, 1995-1996 and 1999-2000.* MMWR Morb Mortal Wkly Rep, 2004. **53**(17): p. 362-5.

2. Parker, S.E., et al., *Updated National Birth Prevalence estimates for selected birth defects in the United States, 2004-2006.* Birth Defects Res A Clin Mol Teratol, 2010. **88**(12): p. 1008-16.

3. March of Dimes, *Global Report on Birth Defects. The hidden toll of dying and disabled children.* 2006, March of Dimes Birth Defects Foundation: White Plains, New York.

4. Botto, L.D., et al., *Neural-tube defects.* N Engl J Med, 1999. **341**(20): p. 1509-19.

5. Yazdy, M.M., et al., *Periconceptional use of opioids and the risk of neural tube defects.* Obstet Gynecol, 2013. **122**(4): p. 838-44.

6. Yazdy, M.M., et al., *Maternal tea consumption during early pregnancy and the risk of spina bifida.* Birth Defects Res A Clin Mol Teratol, 2012. **94**(10): p. 756-61.

7. Parker, S.E., et al., *The impact of folic acid intake on the association among diabetes mellitus, obesity, and spina bifida.* Am J Obstet Gynecol, 2013. **209**(3): p. 239 e1-8.

8. Benedum, C.M., et al., *Risk of spina bifida and maternal cigarette, alcohol, and coffee use during the first month of pregnancy.* Int J Environ Res Public Health, 2013. **10**(8): p. 3263-81.

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: $1,800,000

NCBDDD intends to commit up to $600,000 (including both direct and indirect costs) to fund up to 2 awards for the first 12 month budget period. We anticipate the average award to be approximately $300,000.

An applicant may request a project period of up to three (3) years. The funding amount is estimated to be $300,000 per applicant (including both direct and indirect costs) each year for the 2 nd and 3rd years of the project.

The estimated total funding (direct and indirect costs) for the entire 3 year project period is $1,800,000. An applicant may request a project period of up to 3 years.

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

Anticipated Number of Awards: 2

Applications with budget requests greater than the ceiling will be considered non-responsive and will not be reviewed.

Applications with budget requests less than the floor amount will be considered non-responsive and will not be reviewed.

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

Award Ceiling: $350,000 Per Project Period

Award Floor: $125,000 Per Project Period

Total Project Period Length: 3 year(s)

Throughout the project period, 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 (http://www.hhs.gov/asfr/ogapa/aboutog/hhsgps107.pdf) will apply to the applications submitted and awards made in response to this FOA.

Section III. Eligibility Information

1. Eligible Applicants

Eligibility Category:

State governments
County governments
City or township governments
Special district governments
Independent school districts
Public and State controlled institutions of higher education
Native American tribal governments (Federally recognized)
Public housing authorities/Indian housing authorities
Native American tribal organizations (other than Federally recognized tribal governments)
Nonprofits having a 501(c)(3) status with the IRS, other than institutions of higher education
Nonprofits without 501(c)(3) status with the IRS, other than institutions of higher education
Private institutions of higher education
For profit organizations other than small businesses
Small businesses
Others (see text field entitled "Additional Information on Eligibility" for clarification)

The following types of Higher Education Institutions are always encouraged to apply for CDC support as Public or Private Institutions of Higher Education:

Hispanic-serving Institutions
Historically Black Colleges and Universities (HBCUs)
Tribally Controlled Colleges and Universities (TCCUs)
Alaska Native and Native Hawaiian Serving Institutions

Nonprofits Other Than Institutions of Higher Education:

Nonprofits (Other than Institutions of Higher Education)

Governments:

Eligible Agencies of the Federal Government
U.S. Territory or Possession

Other:

Native American tribal organizations (other than Federally recognized tribal governments)
Faith-based or Community-based Organizations
Regional Organizations
Foreign Organizations: a Foreign Organization is a public or private organization, whether non-profit or for-profit, located in a country other than the United States (U.S.) and its territories that is subject to the laws of the country in which it is located, irrespective of the citizenship of project staff or place of performance. Delete when Foreign Organizations are not allowed to apply

Bona Fide Agents: a Bona Fide Agent is an agency/organization identified by the state as eligible to submit an application under the state eligibility in lieu of a state application. If applying as a bona fide agent of a state or local government, a legal, binding agreement from the state or local government as documentation of the status is required. Attach with "Other Attachment Forms" when submitting via www.grants.gov.

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 include collaborators or consultants from foreign institutions. All applicable federal laws and policies apply.

3. Special Eligibility Requirements

Applicants must:

1. Document their ability to access data from the proposed existing data source(s) for the purposes of the proposed analyses and anticipated/expected publications.
2. Institutions that are funded under FOA #DD13-003 (BD-STEPS) may not propose analysis of NBDPS data under this FOA #DD15-001 due to funding overlap

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 include the following:

1) Provide either of the following:

a) Statement that the applicant institution owns the data or;

b) Letter from an authorized representative of the owner of the data stating that the applicant has access to the data for the purposes of the activities proposed in this application.

2) Statement of applicant showing they are/are not a currently funded grantee under FOA DD13-003 “Cost-Benefit of Incentive-based Smoking Cessation for Pregnant Women”

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

Incomplete applications, applications submitted after 5:00 PM on the listed application due date or non-responsive applications with budgets that exceed the ceiling or with budgets that are below the floor amount of the award will not be entered 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%2 0for%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
- 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 grantee 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 grantee 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/ asfr/ ogapa/ aboutog/ hhsgps107.pdf).

10. Number of Applications

As defined in the HHS Grants Policy Statement, (http://www.hhs.gov/asfr/ogapa/aboutog/hhsgps107.pdf), applications received in response to the same funding opportunity announcement 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 FOA that is essentially the same as one currently pending initial peer review unless the applicant withdraws the pending application.

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 Procurement and Grants Office Technical Information Management Section (PGO TIMS) staff at (770) 488-2700 or pgotim@cdc.gov for further instructions. Hours: Monday - Friday, 7am – 4:30pm U.S. Eastern Standard 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 (http://grants.nih.gov/grants/funding/ 424/SF424_RR_Guide_General_VerC.pdf), except where instructed in this Funding Opportunity Announcement 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 FOA 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 FOA. 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.

3. Letter of Intent

Due Date for Letter of Intent: **01/23/2015**

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 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)
Names of other key personnel
Participating institutions
Number and title of this funding opportunity

The letter of intent should be sent to:

Natalie J. Darling, MPH

Scientific Program Official

National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) and

National Center on Birth Defects and Developmental Disabilities (NCBDDD)

Extramural Research Program Operations and Services

Centers for Disease Control and Prevention

4770 Buford Highway, NE M/S F-80

Atlanta, GA 30341

Telephone: (770) 488-5740

Email: ndarling@cdc.gov

4. Required and Optional Components

A complete application has many components, both required and optional. The forms package associated with this FOA in Grants.gov includes all applicable components for this FOA, 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 Funding Opportunity Announcements (FOAs). Specifically, some of the following 16 components are for Resubmissions or Revisions only. See Part I, Section 5.5 of the SF 424 (R&R) Application Guide (http://grants.nih.gov/grants/funding/424/SF424_RR_Guide_General_VerC.pdf) for additional information. Please attach applicable sections of the following Research Plan components as directed in Part 2, Section 1 (Funding Opportunity Announcement Description).

Follow the page limits stated in the SF 424 unless otherwise specified in the FOA. As applicable to and specified in the FOA, 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 FOA.
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 **unless otherwise specified in the FOA.**

All instructions in the SF424 (R&R) Application Guide (http://grants.nih.gov/grants/funding/424/SF424_RR_Guide_General_VerC.pdf) must be followed along with any additional instructions provided in the FOA.

Research Plan

The applicant's research plan should address activities that will be conducted over the entire 3 year project period and should include the following items:

Data

- A description of the existing data that will be used in the project, including: the study methods used to collect the data; the start and end dates of data collection; and variables available in the data that will be used in analyses for this project. To the extent possible, available data should include case and control status, including some detailed clinical information; demographic factors, such as maternal age, race-ethnicity, and family socioeconomic status; maternal health information; pregnancy information; occupational information; and environmental and residential information.

- The applicant should provide documentation of their authority to access and analyze the data.

- The applicant should demonstrate that the data were collected in areas with established mandatory folic acid, including the date when folic acid fortification began relative to their data collection dates, or that individual-level folic acid intake data are available for the study population. Use of data exclusively or predominantly from the pre-folic acid era (i.e. prior to 1992) is not acceptable.

- A description of the population-base from which spina bifida cases were ascertained. If the study relied only on clinic- or hospital-based selection of cases, evidence must be presented that the approach resulted in a study population representative of the population of children with NTDs with

respect to race-ethnicity, socioeconomic status, etc. in that geographic region.

- A description of how the proposed research utilizes data from existing population-based birth defects surveillance programs of children with NTDs (ICD-9 CM codes 740.0-742.0), with verification of the specific diagnoses from medical record review, autopsy, and cytogenic studies; not based solely on codes.

- The applicant should specify whether they were able to include pregnancies affected by spina bifida that ended in elective termination and stillbirth, in addition to live birth. If stillbirths and elective terminations were not included, the applicant should describe the potential impact of this limitation on the proposed analyses.

- A description of the referent group of pregnancies not affected by spina bifida, including how it is representative of the source population and not a convenience sample.

- If proposing analysis of NBDPS data, applicant must confirm that they are not receiving funding under FOA# DD13-003 (BD-STEPS).

Analyses

- A detailed description of the proposed research methods. Describe how the proposed methods will improve comparability with other studies, and maximize the contribution the project makes to the understanding of modifiable risk and protective factors for folate-resistant NTDs. Specify exposures that will be investigated and describe how they include 1) potentially modifiable factors that have not previously been assessed for their association with spina bifida risk; 2) more refined investigation of previously-identified modifiable risk factors for spina bifida; and/or 3) replication of previously observed associations from population-based studies.

- Description of the available sample size and power calculations to demonstrate adequate statistical power for the proposed analyses.

- A description of how the proposed analyses will incorporate consideration of demographic factors, such as maternal age, race-ethnicity, education, and family socioeconomic status.

- Discuss how the data will be analyzed and by whom.

- A description of how the applicant will publish at least 5 peer-reviewed manuscripts by the end of the 3-year project period on risk factors for spina bifida or other papers furthering the field of spina bifida research.

Management

- A timeline for obtaining IRB approval for the proposed research.

- A proposed timeline of activities over the three year project period. The timeline should detail objectives, measurable steps for project implementation, completion, publications, and presentations and dates by which those objectives will be met.

- Letters of support from potential partners describing commitment of the organization to the project, any specified limits to collaboration, and if applicable, terms of access to data.

- A description of the research team's experience with similar research projects. Evidence of such experience should be provided in the form of publications and/or reports within the last five years.

- A description of how a collaboration with scientific collaborators at CDC will be established.

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.

7. Page Limitations

All page limitations described in this individual FOA must be followed. For this specific FOA, 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 (Part I, Section 2) (http://grants.nih.gov/ grants/funding/424/ SF424_RR_Guide_General_VerC.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 (http://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 CDC PGO TIMS at 770-488-2700; www.pgotim@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 FOA (pgotim@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: **02/24/2015**

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).

11. Funding Restrictions

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.

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

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/ Electronic Receipt /avoiding_ errors.htm or http:// grants. nih.gov/grants/ Electronic Receipt/submit _app.htm

Upon receipt, applications will be evaluated for completeness by the CDC Procurement and Grants Office (PGO) and responsiveness by PGO 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?

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?

- Does the applicant demonstrate experience with similar research projects?
- Does the applicant provide evidence of such experience in the form of publications and/or reports within the last five years?

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?

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?

- 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 for spina bifida, identifying modifying factors for established risk factors for spina bifida, and/or replicating previously observed associations from population-based studies?
- If the proposed project is a domestic study, will the source of the study population be representative of the U.S. population of children with spina bifida with respect to

race-ethnicity, socioeconomic status, etc., or does it focus on a specific high-risk population?

- Does the applicant utilize data from/work with/build on existing population-based birth defects surveillance programs of children with spina bifida with verification of the specific diagnoses from medical review, autopsy, and cytogenetic studies; not based solely on codes?-
- Do the described data source(s) include information to be used for identification of spina bifida cases and controls and folic acid exposure?
- Does the source population for data identified with demonstration that study data, for both cases and controls, show a representation of the source population, with estimates of the numbers of cases and controls and time period provided?
- Is an analytical plan provided for assessing novel risk factors for spina bifida and/or for deeper exploration of potential modifying factors of established risk factors?
- Are power calculations provided that demonstrate the proposed analyses have sufficient statistical power to yield meaningful results?

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?

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/od/pgo/funding/grants/additional_req.shtm#ar1).

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 (http://www.cdc.gov/maso/Policy/Policy_women.pdf and http://www.gpo.gov/fdsys/pkg/FR-1995-09-15/pdf/95-22950.pdf#page=1) and the policy on the Inclusion of Persons Under 21 in Research (http://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

(http://grants.nih.gov/grants/guide/url_redirect.htm?id=11150).

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.

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 Plans
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: http://www.cdc.gov/od/pgo/funding/grants/additional_req.shtm#ar25. Investigators responding to this funding opportunity should include a plan on sharing research resources and data.

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/od/pgo/funding/budgetguide.htm.

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 FOA. 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.
- Number of cases to be included in the study population (i.e., statistical power).

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 FOA 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 (http:// www.hhs.gov/ asfr/ogapa/aboutog/ 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 grantee's business official.

Awardees 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

All HHS/CDC grant and cooperative agreement awards include the HHS Grants Policy Statement as part of the NoA. For these terms of award, see the HHS Grants Policy Statement Part II: Terms and Conditions of Award (http:// www.hhs.gov/ asfr/ogapa/ aboutog/ hhsgps107.pdf).

Awardees must comply with the administrative requirements (AR) outlined in 45 Code of Federal Regulations (CFR) Part 74 or Part 92, as appropriate, as well as any additional requirements included in the FOA.

Specific requirements that apply to this FOA are the following:

Generally applicable ARs:

AR-1: Human Subjects Requirements

AR-2: 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 2010

AR-12: Lobbying Restrictions

AR-14: Accounting System Requirements

AR-16: Security Clearance Requirement

AR-21: Small, Minority, And Women-owned Business

AR-22: Research Integrity

AR-24: Health Insurance Portability and Accountability Act Requirements

AR-25: Release and Sharing of Data

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 - Distinguishing Public Health Research and Public Health Nonresearch

AR 32 –; FY 2012 Enacted General Provisions

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

For more information on the Code of Federal Regulations, visit the National Archives and Records Administration at: http://www.archives.gov/

To view brief descriptions of relevant CDC requirements visit: http://www.cdc.gov/od/pgo/funding/grants/additional_req.shtm

3. Additional Policy Requirements

The following are additional policy requirements relevant to this FOA:

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:

http:// www.hhs.gov/ asfr/ogapa/acquisition/ effspendpol_memo.html)

Federal Funding Accountability and Transparency Act of 2006

Public Law 109-282, the Federal Funding Accountability and Transparency Act of 2006 as amended (FFATA), 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 Web site,

www.USASpending.gov (http:// www.usaspending. gov/). For the full text of the requirements, please review the following website: https:// www.fsrs.gov/.

Plain Writing Act

The Plain Writing Act of 2010 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.

Tobacco and Nutrition Policies

The CDC supports implementing evidence-based programs and policies to reduce tobacco use and secondhand smoke exposure, and to promote healthy nutrition. CDC encourages all awardees to implement the following *optional* evidence-based tobacco and nutrition policies within their organizations. These policies build on the current federal commitment to reduce exposure to secondhand smoke, which includes The Pro-Children Act, 20 U.S.C. 7181-7184 that prohibits smoking in certain facilities that receive federal funds.

Tobacco:

- Tobacco-free indoors – no use of any tobacco products (including smokeless tobacco) or electronic cigarettes in any indoor facilities under the control of the applicant.
- Tobacco-free indoors and in adjacent outdoor areas – no use of any tobacco products or electronic cigarettes in any indoor facilities, within 50 feet of doorways and air intake ducts, and in courtyards under the control of the applicant.
- Tobacco-free campus – no use of any tobacco products or electronic cigarettes in any indoor facilities and anywhere on grounds or in outdoor space under the control of the applicant.

Nutrition:

- Healthy food service guidelines that at a minimum align with Health and Human Services and General Services Administration Health and Sustainability Guidelines for Federal Concessions and Vending Operations for cafeterias, snack bars, and vending machines in any facility under the control of the recipient organization and in accordance with contractual obligations for these services. The following are resources for healthy eating and tobacco free workplaces:

  - http://www.gsa.gov/graphics/pbs/ Guidelines_for_Federal_Concessions_and_Vending_Operations.pdf

  - http://www.cdc.gov/nccdphp/dnpao/hwi/toolkits/tobacco/index.htm

  - http://www.cdc.gov/chronicdisease/resources/guidelines/food-service-guidelines.htm

Applicants should state whether they choose to participate in implementing these two optional policies. However, no applicants will be evaluated or scored on whether they choose to participate in implementing these optional policies.

4. Cooperative Agreement Terms and Conditions of Award

The following special terms of award are in addition to, and not in lieu of, otherwise applicable U.S. Office of Management and Budget (OMB) administrative guidelines, U.S. Department of Health and Human Services (DHHS) grant administration regulations at 45 CFR Parts 74 and 92 (Part 92 is applicable when State and local Governments are eligible to apply), and other HHS, PHS, and CDC grant administration policies.

The administrative and funding instrument used for this program will be the cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial CDC programmatic involvement with the awardees is anticipated during the performance of the activities. Under the cooperative agreement, the HHS/CDC purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; CDC Project Officer are not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and HHS/CDC as defined below.

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

- Providing oversight of the management and administrative aspects of the project, including maintaining an adequate staffing plan to support project activities
- Working collaboratively with CDC scientists on aspects of study design and analysis
- Meeting human subjects' research and IRB requirements, including maintaining current IRB approval until all analyses using these data are complete
- Data storage and management with appropriate protection of confidentiality
- Clinical review of potential cases
- Statistical analysis of data
- Ensuring timely responses to all quality control activities of the study
- Presenting findings from analyses at two or more national scientific meetings beginning in year two
- Dissemination of information to interested parties
- Participating in periodic conference calls to discuss progress of the project, including successes and challenges

Awardees 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.

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

- Additionally, an agency program official or CIO program director will be responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice. There are two separate CDC scientific roles – Scientific Collaborator (SC) and the Scientific Program Official (SPO).

In this cooperative agreement, a CDC Scientist (Scientific Collaborator) within the DBDDD Birth Defects Branch, NCDBBB, is an equal partner/collaborator with scientific and programmatic involvement during the conduct of the project through technical assistance, advice, and coordination. Scientific collaborators will:

- Use their experience in studies of this nature to advise the project on specific questions regarding the project

- Assist the project regarding such areas as data management, data analysis, or other methodological issues
- Provide scientific consultation and technical assistance on questions related to epidemiology, statistical and power calculations, and data storage and tracking formats used in other CDC-sponsored research that could be advantageous to the project.
- Suggest to the project processes for analysis, interpretation, and reporting of findings in the literature that can serve a broad range of scientific interests.
- Obtain IRB approvals as required by CDC when CDC is engaged in research involving human subjects

Areas of Joint Responsibility include:

- Both the recipient and the CDC scientific collaborator will participate in development of publications and dissemination of findings, with both the recipient and the CDC collaborator(s) responsible to serve as co-authors on abstracts, publications, and presentations resulting from the study
- Communicate/coordinate collaborative activities to improve the overall quality of the studies and ensure data quality
- Participate in periodic conference calls to discuss progress and success of the project Plan

5. Reporting

Awardees will be required to submit the Non-Competing Continuation Grant Progress Report (PHS 2590) annually 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 awardees 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 awardees of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later. All awardees 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 (http:// www.hhs.gov/asfr/ ogapa/aboutog/ hhsgps107.pdf) for additional information on this reporting requirement.

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**, (use form PHS 2590, posted on the HHS/CDC website, http:// www. cdc.gov/ od/pgo/ funding/ forms.htm and at http:// grants.nih.gov/grants/ funding/2590/ 2590.htm, **is due 90 to 120 days prior to the end of the current budget period.** 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 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.**
3. **A final progress report**, invention statement, equipment/inventory report, and the final FFR are required **90 days after the end of the project period.**

B. Content of Reports
1. Yearly Non-Competing Grant Progress Report: The grantee's continuation application/progress report should include:

- Description of Progress during Annual Budget Period: Current Budget Period Progress reported on the PHS 2590 (http:// grants1.nih.gov/ grants/funding/ 2590/2590.htm) http:// grants.nih.gov/grants/ funding/2590/2590.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.

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. **All CDC Financial Expenditure data due on/after October 1, 2012 must be submitted using the FFR via the eFSR/FFR system in the eRA Commons.** All Federal Reporting in the Payment Management System is unchanged. All new submissions should be prepared and submitted as FFRs.

CDC's implementation of the FFR retains a financial reporting period that coincides with the budget period of a particular project. However, **the due date for annual FFRs will be 90 days after the end of the calendar quarter in which the budget period ends**. Note that this is a change in due dates of annual FFRs and may provide up to 60 additional days to report, depending upon when the budget period end date falls

within a calendar quarter. For example, if the budget period ends 1/30/2012, the annual FFR is due 6/30/2012 (90 days after the end of the calendar quarter of 3/31/2012). Due dates of final reports will remain unchanged. The due date for final FFRs will continue to be 90 days after the project period end date.

Grantees must submit closeout reports in a timely manner. Unless the Grants Management Officer (GMO) of the awarding Institute or Center approves an extension, grantees 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 grantees are now available at http:// grants.nih.gov/ grants/forms.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: http://www. cdc.gov/od/pgo/ funding/grants/eramain. shtm.

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: http://era.nih.gov/commons/. Organizations not yet registered can go to https:// commons. era.nih.gov/ commons/ registration/ registration Instructions. jsp 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: http:// era.nih.gov/ commons /index.cfm.

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 grantee'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 project period. 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.

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)
Procurement and Grants Office
Telephone 770-488-2700
Email: PGOTIM@cdc.gov
Hours: Monday - Friday, 7am – 4:30pm U.S. Eastern Standard Time

Scientific/Research Contact(s)

Natalie J. Darling, MPH
Scientific Program Official

National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) and NCBDDD

Extramural Research Program Operations and Services

Centers for Disease Control and Prevention

4770 Buford Highway, NE M/S F-80

Atlanta, GA 30341

Telephone: (770) 488-5740
Email: ndarling@cdc.gov

Peer Review Contact(s)
Moises (Chris) Langub, PhD
Scientific Review Official

NCCDPHP and NCBDDD

Extramural Research Program Operations and Services

Centers for Disease Control and Prevention

4770 Buford Highway, NE M/S F-80

Atlanta, GA 30341

Telephone: (770) 488-3585
Email: eeo6@cdc.gov

Financial/Grants Management Contact(s)
Daryl Barksdale

Grants Management Officer (GMO)

NCCDPHP and NCBDDD

Procurement and Grants Office (PGO)

Centers for Disease Control and Prevention

2920 Brandywine Road, MS E-09
Atlanta, GA 30341
Telephone: (770) 488-1087
Email: xxj8@cdc.gov

Section VIII. Other Information

Other CDC funding opportunity announcements 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 Section 301 and 317C of the Public Health Service Act [42 U.S.C. 241, and 247b-4 as amended].

Appendix A. Questions from Potential Applicants and CDC Responses

Q1: I am writing to ask if the recently updated announcement (RFA-DD-15-001) on spida bifida risk factors is open to international setting or the research has to be done in a US population?

A1: Foreign entities are not Eligible Applicants for this FOA. This is referenced in Section III. "Eligibility Information", under "2. Foreign Organizations" in the FOA on page 12. However, a domestic entity could propose individual or comparative studies of domestic and/or international Spina Bifida databases.

Q2: I was wondering if investigating the genetics of spina bifida would be considered a positive vs. negative aim for this FOA? There are different ways to think about genetics but certainly one would be how modifiable risk factors may or may not play a role given someone's genetic makeup. The spina bifida cases that occur in the presence of folic acid may have a genetic susceptibility that has nothing to do with modifiable risk factors.

R2: The FOA's intent is to focus on modifiable risk factors other than folic acid. The FOA does not preclude the type of study you are proposing.

Q3. On page 5 of RFA-DD-15-001 – Public Health Research on Modifiable Risk Factors for Spina Bifida, there is a reference to an Attachment 1; however, it does not appear that the attachment is included in the

announcement - could you send this attachment to us?

R3. In Section I. "Funding Opportunity Announcement Description", under 2.0 "Approach", the 2nd paragraph references "Attachment 1" which was inadvertently omitted from the published FOA. Attachment 1 is included in the amended FOA and is also reprinted below.

Attachment 1*:* Selected Public Health Priorities for the Identification and Confirmation of Spina Bifida Risk Factors Based on Recent CDC-Funded Studies

CONFIRMATION: Associations observed in the National Birth Defects Prevention Study and/or Folic Acid Resistant Spina Bifida Study
Medications - Opioid analgesics - Antihistamines - Ibuprofen - Venlafaxine - Nitrosatable drugs, dietary nitrates, and vitamin C
Diet - Caffeine - Dietary patterns - Diet quality - Micronutrient intake (in addition to folic acid) - Tea consumption
Occupation - Job title - Agricultural pesticides • o Residential pesticides - Polycyclic aromatic hydrocarbons (PAH) - Organic solvents
Other - Cocaine use - Maternal stress and social support - Passive cigarette smoking - Fertility treatments/twinning

MODIFYING: Established risk factors which may be modified by other factors

- Obesity
- Hispanic ethnicity / low acculturation
- Antiepileptic medications
- Diabetes
- Hyperthermia