PROJECT DESCRIPTION: BUILDING ON EXISTING INFRASTRUCTURE OF POPULATION-BASED BIRTH DEFECTS SURVEILLANCE SYSTEMS TO ESTIMATE THE INCIDENCE OF NEONATAL ABSTINENCE SYNDROME (NAS)

This project is funded using federal funds from the Department of Health and Human Services, Centers for Disease Control and Prevention. The project is administrated by the March of Dimes Foundation and is subject to all applicable federal requirements.

Please email any inquiries to: birthdefectsresearch@marchofdimes.org

A. Background and Significance

Neonatal abstinence syndrome (NAS) is a constellation of physiologic and neurobehavioral signs exhibited by newborns exposed to addictive prescription and/or illicit drugs, such as opioids, during pregnancy.[1] Clinical features of NAS include tremors, irritability, high-pitched crying, increased muscle tone, hyperactive deep tendon reflexes, seizures, poor feeding, and gastrointestinal tract dysfunction, all of which contribute to the prolonged hospital stays and high healthcare costs associated with this condition.[1-5] The use, misuse, and abuse of prescription and illicit opioids in the United States have increased dramatically in recent years, particularly among women. With the increasing use of opioids among women, there has been a corresponding rise in infants born with NAS to the point where it is now estimated that every 25 minutes a baby is born suffering from opioid withdrawal in the United States.[4] The national rate of NAS diagnoses increased nearly 5-fold during 2000–2012 and by 2013, NAS incidence among 21 states with publicly available data was estimated to range from 0.7 cases per 1,000 births to 33.4 cases per 1,000 births.[4-6]

The March of Dimes, in collaboration with the Centers for Disease Control and Prevention's (CDC) National Center on Birth Defects and Developmental Disabilities, will provide awards to one to six currently funded state-based birth defects surveillance programs to conduct active (or passive case-finding with case confirmation), population-based surveillance for infants with NAS over a one year period. Additionally, the infants identified with NAS will be followed through one year of age by linking to vital records data (i.e. infant birth and death certificates) and hospital discharge data (i.e., infant's and if possible, mother's delivery records). The main goal of this award will be to obtain state-level, population-based estimates of NAS incidence; awardees also will be asked to monitor hospital readmissions and adverse outcomes among these infants for one year. Programs are expected to select a birth cohort for this project for which they have access to one year of infant hospital discharge data at the time of the award (e.g., if awarded in 2017, some awardees may have ready access to 2015 births and 2015 and 2016 hospital discharge data).

State-based birth defects programs funded through CDC-RFA-DD16-1601 or CDC-RFA-DD16-1605 are eligible to apply if they have an estimated NAS incidence of at least 6 per 1,000 births, a rate higher than the national average.[5] Applicants must provide documentation of their estimated NAS incidence using either: 1) previously-published state-level data (see Ko et al., 2016[6]); 2) previously-published regional data (see Patrick et al., 2015[4]); or 3) other estimates of state-level NAS incidence available to the applicant.

Of note, this funding is intended to support surveillance activities and the development of a summary report that is shared with the March of Dimes, CDC, and other awardees. However,

future analyses and products that involve all partners will be decided upon in a separate process.

Analyses of the NAS cases identified and linked through this funding opportunity have the potential to address these public health questions:

1. How well do diagnosis codes capture infants that actually have NAS (i.e., positive predictive value)?
2. What are the patterns and predictors of health care service use (e.g., number of hospitalizations, length of stay, medication use, and frequency of readmissions up to one year of age) and costs for infants with NAS?
3. What proportion of NAS infants also have birth defects? What specific types of birth defects do NAS infants have?
4. What are demographic characteristics, maternal health conditions, and other adverse outcomes experienced by infants with NAS?

B. Awardee Activities

Awardees will be expected to complete activities in the following project areas: 1) project management and timeline; 2) data linkage, active surveillance (or passive case-finding with case confirmation), and longitudinal follow-up; 3) analysis of the resulting dataset (summary report); 4) collaboration; and 5) grant progress reporting. Each project area is further explained below:

1. Project management and timeline

Awardees will develop a project management plan, including a timeline, for the proposed linkage project. The timeline should include the process for acquiring Institutional Review Board (IRB) approval at the awardee's institution, if required. CDC also will obtain research determination and maintain an IRB approval, if required. The awardee's institutional IRB may defer to the CDC's IRB approval. If the awardee's IRB does not defer to the CDC's IRB, the awardee's IRB will be maintained in addition to the CDC's IRB. For joint academic/state applications, the awardee will be required to include documentation of a planned meaningful collaboration between the state health department and the academic center. Such documentation could include letters of support and/or memoranda of understanding / agreement / engagement and/or data use agreements.

The timeline should state the project's goals and objectives, include month-by-month detailed activities towards meeting those goals and objectives within one year, and clearly identify the responsible parties.

2. Data linkage, active surveillance (or passive case-finding with case confirmation)*, and longitudinal follow-up*

Using existing birth defects surveillance methodology employed in their state, awardees are expected to ascertain cases of NAS for the most recent birth cohort for which one year of infant hospital discharge data are available (e.g., 2015 births with 2015 and 2016 hospital discharge data). Awardees are expected to ascertain neonatal and maternal birth hospitalization information, as well as information on hospital readmissions for infants with NAS for up to one year of age, by linking to vital records data (i.e., infant birth and death

certificates) and hospital discharge data (i.e., infant's and if possible, mother's delivery records).
Active surveillance (or passive case-finding with case confirmation) should be conducted to confirm cases of NAS using the case definition employed in a recent investigation in Florida (see Lind et al, 2015[3]) by identifying infants in the birth cohort with:

a) Presence of a constellation of clinical signs consistent with NAS (i.e., a documented NAS score >8 [on a scale of 0–37]), not explained by another etiology; **and**
b) Documented history of maternal use during pregnancy of prescription or illicit drugs associated with NAS or laboratory confirmation of recent maternal drug use or fetal exposure to such drugs; **and**
c) Severity of illness that resulted in a prolonged (>2 days) neonatal hospitalization.

In addition, awardees are expected to estimate the NAS incidence during the same time period using a passive surveillance methodology by identifying infants with International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes 779.5 (drug withdrawal syndrome in a newborn) and/or 760.72 (noxious influences affecting fetus or newborn via placenta or breast milk, narcotics), as well as ICD, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis code P96.1 (drug withdrawal, infant of dependent mother) if applicable. Thus, the awardee will be able to calculate the positive predictive value (PPV) of NAS ICD-9-CM and ICD-10-CM codes and assess how well these codes identify infants with NAS. Once infants with NAS have been identified and confirmed, they are to be followed through one year of age for readmission and adverse outcomes by linking to vital records data (i.e., infant birth and death certificates) and hospital discharge data (i.e., infant's and if possible, mother's delivery records).

Awardees will collect, link, store, and access data in a secure manner agreed upon by the March of Dimes, CDC, and awardees.

3. Analysis and Summary Report

At the end of the project, the awardees should be able to provide a summary report to March of Dimes and CDC that contains the following information, at a minimum:

- State-level NAS incidence based on an active (or passive case-finding with case confirmation) surveillance methodology
- PPV of ICD-9-CM code 779.5 for identifying NAS
- PPV of ICD-9-CM codes 779.5 and/or 760.72 for identifying NAS
- PPV of ICD-10-CM code P96.1 for identifying NAS (if applicable)
- Health service utilization of NAS infants (neonatal intensive care unit admission, number of hospitalizations, length(s) of stay, medication use, and frequency of readmissions up to one year of age), primary insurance payer, and costs, obtained by linking to hospital discharge data (i.e., infant's and if possible, mother's delivery records).

In addition, ideally awardees will also be able to provide the following information, assuming adequate sample size and compliance with state laws and regulations:

- Characteristics of NAS infants (month of birth, gestational age at birth, infant sex, birth weight, NAS scores/severity, and presence of birth defects and other adverse outcomes, such as reduced head circumference and infant death) obtained by linking NAS

surveillance data to vital records (i.e. infant birth and death certificates) and hospital discharge data (i.e., infant's and if possible, mother's delivery records)

- Maternal characteristics of NAS infants (age, race/ethnicity, types of opioids used during pregnancy, reasons for opioid use, tobacco use, other substance/medication use during pregnancy, Hepatitis C seropositivity, and health conditions/diseases, such as opioid use disorder, HIV, and depression) obtained by linking NAS surveillance data to vital records (i.e. infant birth and death certificates) and hospital discharge data (i.e., infant's and if possible, mother's delivery records)

Only the aggregate, summary data will be shared with the March of Dimes and CDC. No individual-level data will be transferred or stored at the March of Dimes or CDC.

4. Collaboration

Grantees will maintain effective relationships and cooperation with appropriate partners (i.e., state officials, cross-department personnel, including informatics personnel within the state health department, community based organizations, academic medical center(s) and/or treatment center(s) specializing in these conditions) and should plan to collaborate with the March of Dimes and CDC on this project. The March of Dimes and CDC will be actively involved in the project design and plans for any future data analysis. There are likely to be several products from each of the surveillance projects; some projects will be led by the awardees and others may be led by the March of Dimes and/or CDC.

If an analysis is done of the pooled summary data provided at the end of the project period, CDC and March of Dimes, in collaboration with the awardees, will have primary responsibility. Subsequently, each awardee will have primary responsibility for future analyses of the data, with CDC and March of Dimes awarded the opportunity to participate in and lead projects, if desired. **This funding, however, is intended to support surveillance and a summary report as outlined in project activity # 3 but <u>not</u> future analyses.**

5. Grant progress reporting

This is a one-year grant. Both a six-month and end-of-year project report (within 3 months of project completion) will be required. In these reports, the awardees will be expected to detail tasks accomplished toward the stated project goals and objectives, as well as uncompleted planned tasks and provide a rationale for uncompleted tasks. Project reports also will include updates on the NAS surveillance, linkage to vital records and hospital discharge data, results of quality assurance/control procedures in place, lessons learned, and final budget expenditures. Awardees also are expected to participate in regular conference calls with the March of Dimes and CDC collaborators to discuss progress.

C. Timeline and Award

Duration of award: 1 year

Type of funding: Federal, CFDA #93.424

Total funding available: Approximately $230,000

Number of awards: 1-6 awards ranging from approximately $40,000-$70,000 per awardee

RFP publication: January 5, 2017

Bidder's conference call: January 19, 2017

Letter of intent (LOI) due: (required) January 30, 2017

Application due: March 6, 2017

Anticipated award date: May 1, 2017

D. Eligibility Information

This award is open to state-based birth defects programs funded through CDC-RFA-DD16-1601 or CDC-RFA-DD16-1605 that have an estimated NAS incidence of at least 6 per 1,000 births. Applicants must provide documentation of their estimated NAS incidence using either: 1) previously-published state-level data (see Ko et al., 2016[6]); 2) previously-published regional data (see Patrick et al., 2015[4]); or 3) other estimates of state-level NAS incidence available to the applicant.

Eligible applicants include:

- Public/State Controlled Institutions of Higher Education
- Private Institutions of Higher Education
- Nonprofits (Other than Institutions of Higher Education)
- Small Businesses
- For-Profit Organizations (Other than Small Businesses)
- State Governments
- County Governments
- City or Township Governments
- Special District Governments
- Indian/Native American Tribal Governments (Federally Recognized)
- Indian/Native American Tribal Governments (Other than Federally Recognized)
- Eligible Agencies of the Federal Government
- U.S. Territory or Possession
- Independent School Districts
- Public Housing Authorities/Indian Housing Authorities
- Native American tribal organizations (other than Federally recognized tribal governments)

- Faith-based or Community-based Organizations
- Regional Organizations
- 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.

State laws and policies must allow for the release of vital records data and hospital discharge data for surveillance and data linkage purposes. State laws and policies must also allow for the release of pooled data to the March of Dimes and CDC. Applicants whose state laws and policies do not allow for either action will be deemed ineligible.

Applicants must demonstrate an ability to conduct surveillance for NAS and provide a detailed description of their planned process for NAS surveillance. Applicants must also demonstrate their ability to conduct data linkage using surveillance data and other sources. This includes documentation that:

- The applicant has access to the data sources necessary to conduct active (or passive case-finding with case confirmation) surveillance for NAS in their state – i.e., demonstrates access or has a plan in place to obtain access to maternal and infant medical records to ensure that NAS cases meet the case definition.
- The applicant has access to vital records data and demonstrates previous linkages with vital records data
- The applicant has access to hospital discharge data (i.e., infant's and if possible, mother's delivery records) and demonstrates previous linkages with hospital discharge data. The applicant has a clear plan in place for the evaluation of the quality of the proposed surveillance.

Applicants must also provide letters of support or a memorandum of agreement / understanding / engagement, or other documentation from the agency authorized to grant access to each required data source (e.g., data use agreement, if available). The letters of support or agreement must specify all the years for which data are available and state that data access is granted (or will be granted if the applicant is awarded), as well as any limitations regarding data use. If applicable, a copy of these documents should accompany each application.

E. Content and Form of Application Submission

Letter of Intent (LOI)

Letters of intent must be submitted via the March of Dimes eGrants system at http://modresearchgrants.egrant.net.

The LOI must contain a statement of intent to apply, the proposed title of your project, and the contact information of the principal investigator, including phone number, mailing address, organization affiliation, and email address. The letter should not exceed one page.

Application

Applications must be submitted via the March of Dimes eGrants system at http://modresearchgrants.egrant.net. Further instructions for submission will be sent to eligible applicants after the LOI is received.

Additional instructions for completing the application are as follows:

A project abstract must be submitted (350 words or less). The project abstract must contain a summary of the proposed activities suitable for dissemination to a committee of reviewers. It should be a self-contained description of the project and include a statement of objectives and methods to be employed. The project abstract should be informative to other persons working in the same or related fields and insofar as possible understandable to a technically literate lay reader. This abstract must not include any proprietary/confidential information.

A project narrative must be submitted in the following format:

- Maximum number of pages: 20
- Font size: 12 point unreduced, Times New Roman
- Line spacing: Double
- Page margin size: One inch
- Number all narrative pages

The narrative should address activities to be conducted over the entire project period (one year) and must include the following items in the order listed:

A. Background of Surveillance Population, Birth Defects Surveillance System and Public Health Value of NAS Surveillance
B. Plans for NAS Surveillance
C. Plans for Linkage of Vital Records and Hospital Discharge Data with NAS Surveillance Data
D. Capacity of Application to Create Summary Analysis Report
E. Capacity of Applicant to Undertake Project
F. Budget and Budget Justification (The budget and budget justification may be included as a separate attachment, not to be counted in the narrative page limit.)
G. Institutional Signature Form. (The institutional signature form may be included as a separate attachment, not to be counted in the narrative page limit. The form can be found at the end of this document.)

Additional information may be included in the application appendices. The appendices will not be counted toward the narrative page limit. This additional information includes:

- Letters of support, memoranda of understanding / engagement / agreement, or data use agreements (whichever are available and relevant to the specific applicant and linkages proposed)
- NIH-style biosketch of all key personnel
- Timeline and workplan (matrix)
- Documentation of indirect cost agreement, if applicable

F. Evaluation Criteria

Eligible applications will be evaluated against the following criteria:

1. Background of Surveillance Population, Birth Defects Surveillance System and Public Health Value of NAS Surveillance **(15 points)**
    a. To what extent does the applicant describe the composition of the surveillance birth population, including year(s) of data proposed for surveillance, number of births per year by race/ethnicity, type of birth defects ascertained by the surveillance system, and expected NAS incidence? (5 points)
    b. To what extent does the applicant describe how the birth defects surveillance data has been used previously for longitudinal linkage projects for research or non-research activities? (5 points)
    c. To what extent does the applicant clearly articulate the public health value of the proposed surveillance and data linkage? How would the proposed linkages ultimately contribute to the literature and knowledge base? (5 points)

2. Plans for NAS Surveillance **(20 points)**
    a. To what extent does the applicant describe how the birth defects surveillance system could be used as a foundation for NAS surveillance, including the variables ascertained and the capacity to ensure that NAS cases meet the active (or passive case-finding with case confirmation) surveillance case definition? (10 points)
    b. To what extent is the applicant able to conduct passive surveillance for NAS? Does the applicant demonstrate the ability to access (or plans to quickly gain access to) the necessary data from the birth year of interest? (10 points)

3. Plans for Linkage of Vital Records and Hospital Discharge Data with NAS Surveillance Data **(25 points)**
    a. To what extent does the applicant describe the process for linking cases of NAS to vital records and hospital discharge data? Does the applicant demonstrate the ability to access (or plans to quickly gain access to) the necessary hospital discharge data from the follow-up year(s) of interest? Does the applicant provide a list of personal identifiers that they will use to link and an explanation of how they will validate the linkages? Maximum points will be given to applicants that conduct a linkage with known identifiers. (15 points)
    b. Is the overall proposed plan adequate to carry out major project components? Is the timeline provided reasonable and are the objectives SMART (specific, measurable, assigned, realistic, and time-phased)? To what extent does the timeline incorporate major project activities and milestones, including IRB submission(s) and/or approval(s) and development and execution of data use agreements? (10 points)

4. Capacity of Applicant to Create Summary Analysis Report **(20 points)**
    a. To what extent does the application provide evidence of the staff's ability and expertise in producing the requirements of the summary report outlined in Section B.3 of this document? (10 points).
    b. Has the applicant conducted similar analyses in the past? To what extent and with what success? (10 points)

5. Capacity of Applicant to Undertake Project **(20 points)**
    a. To what extent does the applicant provide evidence of the staff's ability and expertise to successfully conduct surveillance and link surveillance data to vital records and hospital discharge data? (10 points)
    b. Has the applicant conducted similar types of studies in the past? To what extent and with what success? (10 points)

6. Budget and Budget Narrative **(Reviewed but not scored)**

7. Institutional Signature Form **(Reviewed but not scored)**

G. References

1. Hudak ML, Tan, RC, The Committee On Drugs, and The Committee On Fetus and Newborn, American Academy of Pediatrics. Neonatal drug withdrawal. *Pediatrics.* 2012;129(2):e540-560.

2. Creanga AA, Sabel JC, Ko JY, et al. Maternal drug use and its effect on neonates: a population-based study in Washington State. *Obstet Gynecol.* 2012;119(5):924-933.

3. Lind JN, Petersen EE, Lederer PA, et al. Infant and maternal characteristics in neonatal abstinence syndrome--selected hospitals in Florida, 2010-2011. *MMWR Morb Mortal Wkly Rep.* 2015;64(8):213-216.

4. Patrick SW, Davis MM, Lehmann CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *J Perinatol.* 2015;35(8):650-655.

5. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. *JAMA.* 2012;307(18):1934-1940.

6. Ko JY, Patrick SW, Tong VT, Patel R, Lind JN, Barfield WD. Incidence of Neonatal Abstinence Syndrome - 28 States, 1999-2013. *MMWR Morb Mortal Wkly Rep.* 2016;65(31):799-802.