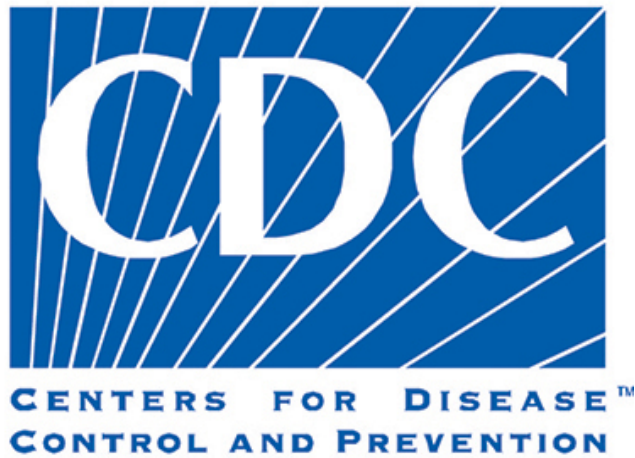




Centers for Disease Control and Prevention

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

Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE): Study to Explore Early Development (SEED) 3

RFA-DD-16-001

Application Due Date: 02/11/2016

Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE): Study to Explore Early Development
(SEED) 3

RFA-DD-16-001

TABLE OF CONTENTS

[Part 1. Overview Information](#)

Key Dates
Required Application Instructions
Executive Summary

[Part 2. Full Text](#)

[Section I. Funding Opportunity Description](#)

[Section II. Award Information](#)

[Section III. Eligibility Information](#)

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

[Section V. Application Review Information](#)

[Section VI. Award Administration Information](#)

[Section VII. Agency Contacts](#)

[Section VIII. Other Information](#)

Part 1. Overview Information

Participating Organization(s)

Centers for Disease Control 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

Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE): Study to Explore Early Development (SEED) 3

Activity Code

U01

Amendment 2 – Responses to questions from potential applicants.

February 1, 2016

Question 1: I wondered if there was any flexibility with the requirements that the catchment area included 40,000 live births in 2014. On page 62 of the SEED3 protocol, it states that sites are assume to have 50% of the potential ASD sources to provide a sample of cases. However, X Hospital provides ASD diagnoses to a majority of children in our catchment area (far more than 50%), but the proposed catchment area has less than 40,000 births. According to the SEED3 protocol children with an ASD diagnosis are not randomly selected (page 40, section ‘a’ of protocol), so it would seem to be appropriate to sample from, for example, our ASD patients.

In summary, we would be able to identify and enroll 125 children with ASD from a catchment area that doesn’t include 40,000 births. If we can demonstrate this, would that be allowed or is the 40,000 live births a firm number? If it is, do you mind describing to me how the number was reached so I can fully understand how the numbers were chosen?

Answer: In the full study protocol (available to all applicants upon request) further explanation is provided that the 40,000 birth population size condition was stipulated because it will be difficult for a site to meet the enrollment target of 125 participants in each study group without this minimum.

Reviewers are thus asked to consider applications in light of the likelihood that the site will be able to enroll sufficient participants to meet the study targets of 125 mother-child pairs in each group who complete the data collection protocol. This includes considering the size of the site’s proposed study area birth population.

While, 40,000 births is not a specific eligibility requirement for this award, applicants proposing to recruit subjects from study areas with smaller birth populations, should take care to explain how they could reasonably meet the study enrollment and completion targets in smaller areas.

Question 2: I am wondering if you could share some cost estimates for some of the SEED protocol steps for our budget planning purposes. Specifically, we are interested in the costs for purchasing and shipping saliva kits and the costs for shipping blood to the central repository. I see in the protocol that blood is shipped in dual temperature kits, but it would be helpful to know if we are to ship with dry ice, overnight/2-day mail, etc. I don't think the Biologic Procedures manual was included in the SEED protocol materials you sent us. Finally, is there a rough estimate of the shipping costs for enrollment packets, maternal interview prep packets, and forms packets?

Answer:

Supplies

Applicants to Component A – SEED Recruitment sites do not need to budget for shippers, blood tubes, or saliva kits. The SEED Central Laboratory and Biosample Repository (CLBR) will purchase these and supply them to the sites.

SEED recruitment sites do need to purchase general phlebotomy supplies such as needles, blood collection sets, tourniquets, gauze, bandages, alcohol pads, sharps containers, biohazard bags, and gloves. Recruitment sites are expected to purchase these items directly from vendors. Access to a centrifuge is required to spin the SST tubes (1000-1300 x g). Also, the shipping packs will need to be refrigerated or frozen before use in the blood sample shipper.

Applicants to Component B – The CLBR must plan in their budget to purchase and ship the following items to sites: purple top EDTA tubes (3 ml), pink top EDTA tubes (6 ml), gold SST tubes (3.5 ml), Paxgene Blood RNA tubes, DNA Genotek Saliva Self-collection kits (OG-500), DNA Genotek Saliva Assisted kits with the swab (OG-575), additional swabs for assisted kits, and shipping materials. Shipping materials will include Category B Combo – Frozen / Refrigerated Shipping Systems, regulation required labels, refrigerant packs, absorbent materials, biohazard bags, bubble wrap pouch for blood tubes, Tyvek envelopes, insulated foil bag envelopes, and medium 95kPa canisters. Please refer to the FOA “Section 2. Approach” and SEED 3 protocol (p. 93-99) “Section H. Study Instrument and Data Collection Method, 7. Clinic Visit Overview (ASD and POP workflows), c. Anthropometry and collect saliva samples” for estimating the number of kits and tubes the CLBR will need to provide to sites.

Shipping

Applicants to Component A – Blood samples are required to be sent via overnight delivery from the recruitment site to the CLBR. Sites are to use the shippers and refrigerant packs provided by the CLBR, no dry ice is required. Shipping costs vary by commercial carrier and distance.

It is up to the recruitment site to decide upon mail carrier for sending forms and other materials to participants. At the GA SEED site, operated by CDC, we often use FedEx to ensure the gift cards are delivered to the correct recipient as well as to ensure delivery of time-sensitive information.

Question 3: This question relates to the developmental testing that takes place during the SEED study visit. When children come to XX Hospital for developmental testing, they undergo a multidisciplinary assessment that includes many of the assessments that are part of SEED3. The question we have is whether we can use the results from this assessment to use for SEED. We see many advantages to leveraging this process—it would mean lower costs, reduced burden on the family and therefore we believe could serve to increase response rates because the requirements for the study visit will be shortened.

Answer: As described in the SEED 3 protocol, developmental assessments must be conducted by individuals meeting certain education qualifications and must be supervised by SEED clinicians also meeting certain education criteria. Moreover, the supervising site clinicians and field clinicians must participate in standardized training procedures and be deemed research reliable according to a priori criteria established for SEED. Additionally, there are established ongoing QC requirements for developmental assessments conducted as part of SEED. Because of the need to ensure standardization across SEED sites and across various phases of SEED, data from developmental assessments conducted previously (before a child enrolls in SEED) are not accepted for this study.

Question 4: We are currently trying to prepare a budget for our SEED 3 application that includes supplies and shipping costs of buccal swabs and venous blood. The FOA seems to indicate we need to budget for these items and the Protocol refers to a Biologic Specimen Manual but it doesn't seem to be included in the protocol appendices that were sent.

Can you provide any more information that would help us anticipate costs related to collecting and processing bio-samples?

Answer:

Supplies

Applicants to Component A – SEED Recruitment sites do not need to budget for shippers, blood tubes, or saliva kits. The SEED Central Laboratory and Biosample Repository (CLBR) will purchase these and supply them to the sites.

SEED recruitment sites do need to purchase general phlebotomy supplies such as needles, blood collection sets, tourniquets, gauze, bandages, alcohol pads, sharps containers, biohazard bags, and gloves. Recruitment sites are expected to purchase these items directly from vendors. Access to a centrifuge is required to spin the SST tubes (1000-1300 x g). Also, the shipping packs will need to be refrigerated or frozen before use in the blood sample shipper.

Applicants to Component B – The CLBR must plan in their budget to purchase and ship the following items to sites: purple top EDTA tubes (3 ml), pink top EDTA tubes (6 ml), gold SST tubes (3.5 ml), Paxgene Blood RNA tubes, DNA Genotek Saliva Self-collection kits (OG-500), DNA Genotek Saliva Assisted kits with the swab (OG-575), additional swabs for assisted kits, and shipping materials. Shipping materials will include Category B Combo – Frozen / Refrigerated Shipping Systems, regulation required labels, refrigerant packs, absorbent materials, biohazard bags, bubble wrap pouch for blood tubes, Tyvek envelopes, insulated foil bag envelopes, and medium 95kPa canisters. Please refer to the FOA “Section 2. Approach” and SEED 3 protocol (p. 93-99) “Section H. Study Instrument and Data Collection Method, 7. Clinic Visit Overview (ASD and POP workflows), c. Anthropometry and collect saliva samples” for estimating the number of kits and tubes the CLBR will need to provide to sites.

Shipping

Applicants to Component A – Blood samples are required to be sent via overnight delivery from the recruitment site to the CLBR. Sites are to use the shippers and refrigerant packs provided by the CLBR, no dry ice is required. Shipping costs vary by commercial carrier and distance.

It is up to the recruitment site to decide upon mail carrier for sending forms and other materials to participants. At the GA SEED site, operated by CDC, we often use FedEx to ensure the gift cards are delivered to the correct recipient as well as to ensure delivery of time-sensitive information.

In addition, applicants to Component B must include in their budget the costs for: extracting DNA; extracting RNA; purchasing, creating, and storing Guthrie blood spot cards; and creating and storing frozen biospecimens.

Amendment 1 -- Sections with changes are noted in bold red in the text below.

January 11, 2016

Part 1. Overview Information

Executive Summary:

Budget and Project Period: The estimated total funding (direct and indirect) for the entire project period, (07/01/2016 – 06/30/2021), is \$21,600,000.

Component A (SEED-3): The estimated total funding (direct and indirect) for the first budget period, (07/01/2016 – 06/30/2017), is \$3,200,000. The estimated total funding (direct and indirect) for the entire 5-year project period, (07/01/2016 – 06/30/2021), is \$17,600,000. Estimated Number of Awards: up to 4. Average amount of each award is YR 1: \$800,000 YRS 2-5: \$900,000.

Component B (Biorepository for SEED-3): The estimated total funding (direct and indirect) for the first budget period, (07/01/2016 – 06/30/2017), is \$300,000. The estimated total funding (direct and indirect) for the entire 5-year project period, (07/01/2016 – 06/30/2021), is \$1,500,000. Estimated Number of Awards: 1. Average amount of each award for YRS 1-5: \$300,000.

Component C (Follow-up Study): The estimated total funding (direct and indirect) for the first budget period, (07/01/2016 – 06/30/2017), is \$500,000. The estimated total funding (direct and indirect) for the entire 5-year project period, (07/01/2016 – 06/30/2021), is \$2,500,000. Estimated Number of Awards: up to 2. Average amount of each award for YRS 1-5: \$250,000.

Part 2. Full Text

Section II. Award Information

Estimated Total Funding:

Component A (SEED-3): The estimated total funding (direct and indirect) for the first budget period, (07/01/2016 – 06/30/2017), is \$3,200,000. The estimated total funding (direct and indirect) for the entire 5-year project period, (07/01/2016 – 06/30/2021), is \$17,600,000. Estimated Number of Awards: up to 4. Average amount of each award: YR 1: \$800,000 YRS 2-5: \$900,000.

Component B (Biorepository for SEED-3): The estimated total funding (direct and indirect) for the first budget period, (07/01/2016 – 06/30/2017), is \$300,000. The estimated total funding (direct and indirect) for the entire 5-year project period, (07/01/2016 – 06/30/2021), is \$1,500,000. Estimated Number of Awards: 1. Average amount of each award: YRS 1-5: \$300,000.

Component C (Follow-up Study): The estimated total funding (direct and indirect) for the first budget period, (07/01/2016 – 06/30/2017), is \$500,000. The estimated total funding (direct and indirect) for the entire 5-year project period, (07/01/2016 – 06/30/2021), is \$2,500,000. Estimated Number of Awards: up to 2. Average amount of each award: YRS 1-5: \$250,000

Part 2. Full Text

Section II. Award Information

Anticipated Number of Awards:

The estimated total funding (direct and indirect) for the first budget period, (07/01/2016 – 06/30/2017), is \$4,000,000. The estimated total funding (direct and indirect) for the entire 5-year project period, (07/01/2016 – 06/30/2021), is \$21,600,000.

Part 2. Full Text

Section VIII. Other Information

Appendix A: SEED 1,2,3,4, Comparison Tables

Field work enrollment time period 2017 -2021

Field work data collection time period 2017 -2021

Funding Opportunity Announcement Type

New

Funding Opportunity Announcement Number

RFA-DD-16-001

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

93.073

Category of Funding Activity:

Health

FOA Purpose

This Funding Opportunity Announcement (FOA) is for applicants to support:

Component A) continuation of the epidemiological research capability of the Centers for Autism and Developmental Disabilities Epidemiology (CADDRE) Network with implementation of the Study to Explore Early Development (SEED) Phase 3.

SEED is a case-control study of genetic and environmental risk and protective factors for autism with multiple-source ascertainment of case and comparison groups; SEED Phase 3 is a continuation of SEED 1 and SEED 2 with the same basic study design but with some enhancements in study recruitment and some reductions in data collection.

Component B) implementation of the SEED Central Laboratory and Biosample Repository (CLBR) to support the maintenance and storage of the SEED Phase 1 and Phase 2 biosample repository and support the collection and storage of the SEED Phase 3 biosamples.

Applicants who apply for **Component A** may also apply for **Component B**.

Component C) development and implementation of a study protocol and feasibility assessment for a follow-up study of SEED 1 participants.

Component C is a project to develop and implement a short protocol and feasibility assessment for conducting a follow-up of the children who enrolled in SEED 1 and completed the SEED 1 study data collection protocol.

Key Dates

Publication Date: To receive notification of any changes to RFA-DD-16-001, 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: 01/04/2016

Is a LOI: Recommended but not Required

Application Due Date: 02/11/2016

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: 04/07/2016

Secondary Review: 05/12/2016

Estimated Start Date: 07/01/2016

Expiration Date: 02/15/2016

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.** CDC has previously implemented a population-based epidemiological research study known as the Study to Explore Development (SEED). Data collection for SEED 1 is complete, data collection for SEED 2 is ongoing. The primary objectives of SEED are 1) to characterize the autism behavioral phenotype and associated developmental, medical and behavioral conditions of autism, with a special focus on identifying homogeneous autism subgroups for etiologic analysis, and 2) to understand the genetic and environmental risk factors for autism with a special focus on immunological, hormonal, obstetric, gastrointestinal and socio-demographic features. The focus of SEED is on preconception, prenatal, perinatal and early postnatal risk factors.

The activities under this FOA will be supported by three separate funding components:

1. **Component A: CADDRE SEED Phase 3** to support the continuation of the epidemiological research capability of the Centers for Autism and Developmental Disabilities Epidemiology (CADDRE) network with implementation of a new Phase of the Study to Explore Early Development (SEED) Phase 3. The intent of this component is to carry out SEED Phase 3 with the same basic study design as SEED 1 and SEED 2 but with enhanced recruitment strategies to improve response rates, and a further reduction in the data collection protocol. Maintaining the same basic study design and overall protocol integrity will ensure that data pooling can be achieved across SEED phases. Both new sites and former SEED sites are encouraged to apply for this component.
2. **Component B: Biorepository** an award for implementation of the SEED Central Laboratory and Biosample Repository. The objectives of Component B of this FOA are to support the maintenance and storage of the SEED Phase 1 and Phase 2 biosample repository and support the collection and storage of the SEED Phase 3 biosamples. It is CDC's goal that all SEED biosamples (from Phases 1, 2, and 3) will be stored in one repository. To be funded for **Component B**, applicants must have a responsive application for **Component A** and receive **Component A** funding.
3. **Component C: SEED 1 Follow-up Study** is a project to develop and implement a short protocol and feasibility assessment for conducting a follow-up of the children who enrolled in SEED 1 and completed the SEED 1 study data collection protocol. Both new sites, and former SEED 1 sites are encouraged to apply for this component. New sites must develop and submit agreements with one or more former SEED 1 sites to fully access all data needed to successfully conduct the follow-up study. Former SEED 1 sites may also propose follow-up of SEED 1 participants from other sites (in addition to their own) to maximize the sample size for this study. If former sites propose working with other SEED 1 sites, they must also develop and submit agreements documenting full data access.

Applicants should clearly indicate the Components for which they are applying and should include at the beginning of the title, the respective component under which the application should be considered (i.e., **Component A**, **Component B**, or

Component C).

- **Mechanism of Support.** Cooperative agreement
- **Funds Available and Anticipated Number of Awards.** The estimated total level of funding (direct and indirect for entire project period in dollars) that is available for the FOA is \$21,600,000 to support up to 7 anticipated awards (over the 3 components). Awards issued under this FOA are contingent upon availability of funds and a sufficient number of meritorious applications. The total amount awarded and the number of awards will depend upon the number, quality, and cost of the applications received.
- **Budget and Project Period.** The estimated total funding (direct and indirect) for the first budget period, (07/01/2016 – 06/30/2017), is \$4,000,000. The estimated total funding (direct and indirect) for the entire project period, (07/01/2016 – 06/30/2021), is \$21,600,000.
- **Component A (SEED 3):** The estimated total funding (direct and indirect) for the first budget period, (07/01/2016 – 06/30/2017), is \$3,200,000. The estimated total funding (direct and indirect) for the entire 5-year project period, (07/01/2016 – 06/30/2021), is \$17,600,000. Estimated Number of Awards: up to 4. Average amount of each award is YR 1: \$800,000 YRS 2-5: \$900,000.
- **Component B (Biorepository for SEED-3):** The estimated total funding (direct and indirect) for the first budget period, (07/01/2016 – 06/30/2017), is \$300,000. The estimated total funding (direct and indirect) for the entire 5-year project period, (07/01/2016 – 06/30/2021), is \$1,500,000. Estimated Number of Awards: 1. Average amount of each award for YRS 1-5: \$300,000.
- **Component C (Follow-up Study):** The estimated total funding (direct and indirect) for the first budget period, (07/01/2016 – 06/30/2017), is \$500,000. The estimated total funding (direct and indirect) for the entire 5-year project period, (07/01/2016 – 06/30/2021), is \$2,500,000. Estimated Number of Awards: up to 2. Average amount of each award for YRS 1-5: \$250,000.
- **Application Research Strategy Length:** Page limits for the Research Strategy are clearly specified in [Section IV. Application and Submission Information](#) of this announcement.
- **Eligible Institutions/Organizations.** Institutions/organizations listed in [Section III. 1.A.](#) are eligible to apply.
- **Eligible Project Directors/Principal Investigators (PDs/PIs).** Individuals with the skills, knowledge, and resources necessary to carry out the proposed research are invited to work with their institution/organization to develop an application for support. NOTE: CDC does not make awards to individuals directly. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply.
- **Number of PDs/PIs.** Applications may include more than one PI; however, the first PI listed on the application will be the “contact PI” for all correspondence. Any additional PIs are permitted, but would be referred to as Co-PIs.
- **Number of Applications.** Only one application per institution (normally identified by having a unique DUNS number) is allowed for each component.”
- **Application Type.** New
- **Special Date(s).** N/A
- **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

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

1. Background and Purpose

This FOA addresses new activities for the Study to Explore Early Development (SEED). SEED is a case-control study of risk and protective factors for autism spectrum disorder (ASD). Under this FOA, CDC will fund the third wave of data collection for the core SEED protocol, support a biorepository and sample processing for the saliva and blood specimens collected as part of the core SEED protocol, and initiate a brief follow-up of the first wave of SEED participants (SEED 1).

Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders characterized by qualitative impairments in social interaction and communication and stereotyped behaviors and interests. Recent systematic population surveys and routine

monitoring systems in the US and other countries indicate the prevalence to be 1% to 2%. Accompanying advances in population-based monitoring of autism prevalence have been changes in diagnostic criteria and development of improved clinical methods, including growth in the number of standardized behavioral assessment tools, for autism screening and diagnosis. Yet, apart from the identification of some rare genetic conditions that are commonly associated with autism, causal mechanisms for the disorder largely remain unknown.

Overview of Funding History for SEED

The Children's Health Act of 2000 mandated CDC to establish autism surveillance and research programs to address the number, incidence, and causes of autism and related developmental disabilities. Under the provisions of this act, NCBDDD funded five Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) through program announcements in FY2001 and FY2002 (California, Colorado, Maryland, North Carolina and Pennsylvania); CDC's NCBDDD served as the sixth CADDRE site.

For the first funding cycle (2001-2006), each CADDRE grantee had three core objectives: to develop a protocol for a multi-site collaborative epidemiologic study focused on autism (which was eventually named the Study to Explore Early Development [SEED]); to conduct surveillance of autism and other developmental disabilities; and to conduct site-specific investigator-initiated studies on autism. In FY 2006, through a second CADDRE funding cycle, five grantees were awarded. The CADDRE activities for the second funding cycle (2006-2011) were limited to implementation of the first phase of SEED (subsequently known as SEED 1). CDC served as the sixth CADDRE SEED 1 site during this period. A second phase of SEED (SEED 2) was funded under a third funding cycle (2011 – currently ongoing with completion in 2016). Five CADDRE grantees received the awards. Again, CDC served as the sixth SEED 2 site.

Both SEED 1 and 2 had the same primary scientific aims:

1. To characterize the autism behavioral phenotype and associated developmental, medical and behavioral conditions of autism, with a special focus on identifying homogeneous autism subgroups for etiologic analysis, and
2. To understand the genetic and environmental risk factors for autism with a special focus on infectious, immunological, hormonal, obstetric, gastrointestinal and socio-demographic features.

SEED Study Design

SEED uses a case-control design with multiple-source, population-based ascertainment of case and comparison groups. Cases (ASD group) comprise children meeting study definitions for ASD (see below). Two different control groups are enrolled: a group of children sampled from the general population (POP) and a comparison group of children with developmental disabilities other than ASD (DD group). Comparisons between ASD and POP are designed to identify risk factors for ASD relative to children in the general population. Comparisons between ASD and DD may provide the opportunity to distinguish risk factors for ASD independent of factors common to other developmental problems. The DD group also provides a means of controlling for recall bias that may arise more commonly among parents of children with developmental problems than among parents of typically developing children.

All three waves of SEED use the same basic study design. However, the SEED 2 protocol incorporated several revisions to the SEED 1 protocol including minor changes in eligibility criteria, recruitment strategies, and participant incentives, and a moderately streamlined data collection protocol. The SEED 3 protocol has been further streamlined in comparison to SEED 1 and 2.

A brief description of the differences between SEED 1 and SEED 2 protocols is provided below. A description of the additional revisions made to the SEED 3 protocol is provided in the following section, APPROACH. Also, Appendix A: SEED SUMMARY TABLES - contains summary tables that compare the three study waves.

Summary of SEED 1 and SEED 2 Protocols

Children were potentially eligible for SEED 1 if:

1. They were born in a study catchment area during the SEED 1 specified birth year range,

- 2 Still resided in the study catchment area during study implementation,
- 3 Lived with a knowledgeable caregiver (family member/caregiver of legal age who resided with and consistently cared for the child since s/he was aged 6 months or younger)
- 4 The knowledgeable caregiver was competent to communicate orally in English (or at two sites, in English or Spanish) and give consent; and
- 5 The child was physically able to complete developmental assessments. To remain eligible, enrolled children must also have been aged 30 to 68 months at the completion of the clinical developmental assessment to maintain the appropriate age range for validated study instruments.

Eligibility criteria for SEED 2 were the same as those for SEED 1 with one exception. In SEED 2 the requirement to live with a knowledgeable caregiver was narrowed to the biological mother. The reason for this revision was to ensure data on key pregnancy exposures were obtained on all SEED 2 participants.

In both SEED 1 and SEED 2, both potential ASD and DD children were ascertained through multiple sources serving or evaluating children with developmental problems, including early intervention, special education and related service programs for toddlers and young children, state autism registries, hospitals, clinics, and individual providers. Potential participants met specific criteria for ASD or an ASD-related exceptionality from early intervention/special education services (e.g., intellectually disabled, severe emotional disorder), or had received an ASD or ASD-related diagnosis or a diagnosis of one or more select conditions associated with ASD (e.g., conduct disorder, intellectual disability, significant developmental delay) from a clinical provider. This broad diagnostic net (“broad net”) for ascertainment of potential ASD cases ensured that both previously diagnosed and undiagnosed cases were identified. Parents who had a child with a documented ASD or ASD-related diagnosis/exceptionality could also contact the study directly and be considered for inclusion. Population control children were identified by randomly sampling state birth certificates of children born in the specified birth date range to mothers resident in a defined catchment area at delivery.

An invitation packet, written in English (and Spanish at two sites), was mailed to the primary caregiver (SEED 1) or biological mother (SEED 2) of all potentially eligible participants. Non-responders received a second invitation letter or were contacted via telephone call or email (9 attempts), depending on the site. During the study introductory telephone call, SEED staff members screened potential participants for eligibility. The Social Communication Questionnaire (SCQ), a 5-10 minute interview, was subsequently administered to the primary caregiver/biological mother of eligible participants to identify children who required a clinical diagnostic evaluation to determine final case status. Children with positive screens or a previous ASD diagnosis/exceptionality were assigned to the ASD workflow. DD or POP children with negative screens were assigned to the DD or POP workflow, respectively. Children in all 3 groups were seen in person for developmental evaluations; however the children in the ASD workflow received a much more extensive evaluation than the children in the DD and POP workflows.

Final participant classifications were dependent on the child’s ascertainment source (i.e., broad net or birth certificate), workflow classification and, for children in the ASD workflow, the results from both the Autism Diagnostic Observation Schedules (ADOS) (Lord et al. 2000, 2003) and the Autism Diagnostic Interview–Revised (ADI-R) (Le Couteur et al. 2003; Lord et al. 1994, 1997) administered during the SEED clinical diagnostic evaluation. SEED final participant classifications included: 1) Final ASD case, 2) Possible ASD case, 3) Final DD, and 4) Final POP.

Extensive data were collected via multiple modalities to address the SEED primary and secondary scientific aims: telephone interviews, self/parent-administered instruments, clinic visits for developmental evaluations and measurement of standard growth parameters, biosampling, and medical record abstraction. Support in completing self/parent-administered forms was provided as needed to overcome literacy barriers.

Data collection was uniform across all participants except that those in the ASD workflow completed additional instruments to assess specific ASD features.

The protocol for SEED 2 data collection was similar to the SEED 1 data collection protocol; however the data collection protocol was notably streamlined in SEED 2. Differences and similarities in data collected in SEED 1 and SEED 2 include the following:

- Both SEED 1 and SEED 2 protocols included the SCQ screener, Child Behavior Checklist, Child Social Responsiveness Scale, Mullen Scales of Early Learning, Vineland Adaptive Behavior Scale, ADOS, ADI-R, and medical record abstractions (prenatal care and labor and delivery records from mother and neonatal care and pediatric care from child). The aforementioned forms were not modified between SEED 1 and SEED 2.
- Both SEED 1 and SEED 2 protocols included an extensive maternal telephone interview that included questions on the mother’s reproductive history and her pregnancy with the index child, maternal and paternal medical history forms, and a

child services and treatment form. These forms were similar between the two study phases; however some revisions were made.

- Biosamples were collected in both SEED 1 and SEED 2 from the child, mother, and father if available. However, in SEED 1 buccal and blood specimens were collected and in SEED 2 saliva and blood specimens were collected to increase the DNA yield. Additionally hair specimens were collected in SEED 1 only.
- Two forms were added to the SEED 2 protocol – a brief residential history form to allow for better assessment of potential environmental exposures and a child health history form. Of **NOTE:** much of the child health history form is comprised of various questions from some of the SEED 1 forms that were dropped from the SEED 2 protocol (below).
- Several forms and examinations included in SEED 1 were dropped from the SEED 2 protocol. These include: the parental Social Responsiveness Scale forms; the Carey Temperament Scale; the Early Development Questionnaire; the family autoimmune disease history form; the paternal occupational exposure form; the child gastrointestinal questionnaire; the child sleep history questionnaire; the child diet diary; and the child stool diary. Of **NOTE:** select questions from the SEED 1 family autoimmune form, parental occupational form, child gastrointestinal form, and child sleep history forms were incorporated into the SEED 2 maternal, paternal, and child health history forms. Thus some key components of some of the “dropped” forms were retained in SEED 2 in a streamlined fashion.
- SEED 1 included a child dysmorphology examination. In SEED 2 this assessment was dropped; however, basic growth parameter measurements were still collected in SEED 2.

For most SEED components (both SEED 1 and SEED 2), Quality Control (QC) procedures and standards were established a priori, including a variety of training exercises, initial “in-the-field” standards, and ongoing standards.

SEED established a Central Laboratory and Biologic Repository for initial processing and archiving of SEED biosamples and a Data Coordinating Center to develop, host and support the CADDRE Information System (CIS), a web-based application developed exclusively for CADDRE. The CIS provides the mechanisms for managing workflow and data processing through the course of the study. All participant data were entered into CIS by SEED staff and securely stored in a HIPAA-class facility. The CIS data from SEED 1 have subsequently been exported into analytic data files which are available to the SEED investigators. Personally identifiable information (PII) is not included in the SEED analytic data files. SEED 2 CIS data will be similarly exported into analytic files and harmonized with SEED 1 data at the completion of the SEED 2 study phase.

In all, 3769 children and their caregivers were enrolled in SEED 1 and 2600 completed nearly all study steps. As of May 2014, 3250 families were enrolled in SEED 2 and 1971 had completed most study steps.

The SEED study sample sizes obtained through SEED 1 and SEED 2 are deemed sufficient for many principal analyses but are not sufficient for more detailed assessment of some key exposure subsets with low population prevalence, assessment of associations within important case subgroups, and many genetic analyses.

Rationale for SEED 3

This FOA to support SEED 3 will enhance our understanding of the genetic and environmental risk and protective factors for autism by building on the established SEED data resource. Implementing a third round of SEED data collection will increase the total SEED pooled sample size for investigation of high priority hypotheses thereby enhancing SEED’s analytic potential. Maintaining the same basic study design and general protocol integrity will ensure that data pooling can be achieved across SEED phases for this purpose.

Modifications that will be implemented in the third round of data collection will include recruitment from a more recent cohort of children, strategies to improve response rates, and a further reduction in the data collection protocol.

Rationale for SEED 1 Follow-up Study

The children already enrolled in SEED 1 and SEED 2 represent a unique opportunity to better understand the long term trajectory of children identified as having autism at early ages. SEED includes one of the largest cohorts of children assembled with ASD. Moreover, given the wealth of health, developmental, and risk factor data collected on both the children and parents included in the core SEED protocol, a follow-up study of the children presents unparalleled opportunities to better understand ASD etiologic subgroups, the long term health and functioning of children with ASD and other DDs, family impacts associated with ASD and other DDs, and service needs and use associated with ASD and other DDs.

In 2016, the oldest SEED children (SEED 1 children) will be adolescents – aged 11 to 14 years. This is an ideal time to begin a

follow-up study as there are many gaps in the current scientific literature on the developmental trajectory and health consequences of ASD among adolescents. Additionally, beginning a follow-up study when the children are adolescents, allows investigators to incorporate methods into the protocol to remain in contact with the children and their families into adulthood and thus possibly continue the initial follow-up into a longer term longitudinal follow-up of children with ASD.

An ancillary benefit of the SEED follow-up study is that will also allow investigators to obtain important consents from SEED 1 families. SEED (as well as nearly all individual studies) are under-powered to address many important questions about genetics. In the years subsequent to the launch of SEED 1, genetic research consortiums have been established to allow genetic data from various studies of ASDs to be pooled. Because such consortia were not in existence when SEED 1 was planned and implemented, SEED participants were not appropriately consented to allow their genetic data (obtained from biosamples collected during SEED 1) to be shared in this manner.

The CDC IRB recently reviewed the SEED 1 consent forms, the current NIH guidance on submitting genetic data into biorepositories, and recent advances in technology that allow for potential identification of individuals based on their genetic data. They determined that the existing SEED 1 consents do not sufficiently address the issue of genetic data sharing. A SEED follow-up study will provide an opportunity to obtain from SEED 1 participants specific consents for genetic data sharing and thus maximize the use of the SEED biorepository data.

Healthy People 2020 and other National Strategic Priorities

This RFA addresses “Healthy People 2020” priority area(s) of Maternal, Infant, and Child Health and is in alignment with NCBDDD performance goal(s) to prevent birth defects and developmental disabilities.

(<http://www.healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?topicId=26>)

Public Health Impact

The prevalence of ASD is estimated to be 1% to 2%. Apart from the identification of some rare genetic conditions that are commonly associated with autism, causal mechanisms for the disorder largely remain unknown. SEED was developed to address important scientific aims:

- 1) To characterize the autism behavioral phenotype and associated developmental, medical and behavioral conditions of autism, with a special focus on identifying homogeneous autism subgroups for etiologic analysis, and
- 2) To understand the genetic and environmental risk factors for autism with a special focus on infectious, immunological, hormonal, obstetric, gastrointestinal and socio-demographic features.

This FOA to support the implementation of a third round of SEED data collection will increase the total SEED pooled sample size for investigation of high priority hypotheses thereby enhancing SEED’s potential to investigate ASD risk factors.

This FOA also supports the development and implementation of a SEED 1 follow-up study, which represents a unique opportunity to better understand the long term trajectory of children identified as having autism at early ages. Given the wealth of health, developmental, and risk factor data collected on both the children and parents included in the core SEED protocol, a follow-up study of the children will advance our understanding of ASD etiologic subgroups, the long term health and functioning of children with ASD and other DDs, family impacts associated with ASD and other DDs, and service needs and use associated with ASD and other DDs. The data generated from this follow-up study will directly impact public health program planning.

Relevant Work

CDC currently funds five CADDRE/SEED sites through cooperative agreements (current funding scheduled to end June 2016). Each funded site in the CADDRE/SEED network conducts autism research and is required to enroll a specific number of participants in each population group (CASE, DD, and POP). The data collected by the sites is entered into the CADDRE Information System (CIS) that is managed by a data coordinating center funded by the CDC. CDC provides scientific oversight for both the SEED project and the data coordinating center.

CADDRE principal investigators worked collaboratively with CDC to develop the original SEED protocol as well as the current SEED protocol. Multiple working groups were established by CADDRE in SEED 1 to organize and develop this large and multi-faceted case-control study. These working groups were retained in SEED 2 and will also be retained in SEED 3.

2. Approach

To meet the goals of the FOA, this announcement includes 3 separate funding components:

1. **Component A: CADDRE SEED Phase 3** a continuation of the core SEED project with implementation of a new SEED Phase 3 using a new streamlined protocol.
2. **Component B: SEED Central Laboratory and Biosample Repository**; implement and serve as laboratory and biosample repository for SEED Phase 3 study sites and serve as biosample storage source for SEED 1 and SEED 2. To be funded for **Component B**: Applicants must have a responsive application for **Component A** and receive **Component A** funding.
3. **Component C: SEED 1 Follow-up Study** development and implementation of a study protocol and feasibility assessment for a follow-up study of SEED 1 participants.

Applications should clearly indicate the Component for which the applicant is applying and should include at the beginning of the title, the respective component under which the application should be considered (i.e., **Component A, Component B, or Component C**).

Objectives/Outcomes

Component A: CADDRE SEED Phase 3

The intent of this component is to carry out SEED Phase 3 with the same basic study design as SEED 1 and SEED 2 but with enhanced recruitment strategies to improve response rates, and a further reduction in the data collection protocol.

High priority scientific areas of interest for SEED Phase 3 remain the same as for SEED 1 and SEED 2 and include:

- 1) Characterize the autism behavioral phenotype and associated developmental, medical and psychiatric conditions of autism, with a special focus on identifying homogeneous autism subgroups for etiologic analysis, and
- 2) Understand the genetic and environmental risk factors for autism with a special focus on immunological, hormonal, obstetric, and socio-demographic features. Secondary areas of scientific interest will include investigation of the association of autism and maternal lifestyle factors in pregnancy (tobacco, alcohol and recreational drug use), maternal and paternal occupational history proximal to and during pregnancy, maternal residential history proximal to and during pregnancy, and assessment of child postnatal health characteristics.

Applicants under this FOA should describe how they will carry out the SEED Phase 3 protocol including:

- 1) Specific study population and catchment area;
- 2) Recruitment strategies;
- 3) Data collection and quality control procedures;
- 4) Collaboration with CDC and other sites through active participation in work groups and committees;
- 5) Collaboration with the designated SEED Data Coordinating Center and Central Laboratory and Biorepository; and
- 6) Data analysis and dissemination of findings.

Maintaining the same basic study design and overall protocol integrity will ensure that data pooling can be achieved across SEED phases.

A copy of the complete SEED 3 protocol is available upon request see *Section VII. Agency Contacts, Scientific / Research Contact(s) Michael A. Brown* to obtain a copy of the SEED 3 protocol.

This protocol is very similar to the SEED 2 protocol. However, some enhancements have been added to increase response rates and better understand response bias. These include language encouraging sites to work closely with their local data sources to develop mechanisms to increase response to the initial invitation mailing and obtain the necessary permissions to implement these mechanisms. The exact mechanism will vary by site but incorporating some type of active follow-up of non-responders via telephone calls, email messages, or both is strongly encouraged.

The second enhancement added to the SEED 3 protocol is language that sites are strongly encouraged to develop a mechanism and obtain necessary permissions to allow for linkage of limited birth certificate data on all participants (ASD, DD, and POP groups) invited including those who are never successfully contacted, those who refuse contact, and those contacted but found to be ineligible such that SEED investigators will be able to directly assess characteristics of respondents vs. non-respondents.

The exact plan for data linkage can vary across sites. Some sites will have access to the full birth records and are thus able to perform linkages between children invited from the ASD and DD source lists directly and retain all of the data onsite. Other sites might obtain more limited access. While individual-level data is preferred, aggregate data with distributions of aforementioned key variables will also be helpful in assessing potential response bias.

There are no other additions to the SEED 3 protocol. However, there are some reductions; the SEED 3 data collection protocol is a more streamlined version of the SEED 2 data collection protocol.

A summary of the main components of the SEED 3 protocol is described below and also can be found in the Tables included in Appendix A.

SEED 3 Study Design and Recruitment:

- The SEED case-control design, including an ASD case group and DD and POP comparison groups at a 1:1 ratio of the ASD case group to the DD comparison group and a 1:1 ratio of the ASD case group to the POP comparison group, will be retained.
- SEED's original multi-source, population-based ascertainment approach for potential ASD and DD participants, including use of the "broad diagnostic net" to ensure both previously diagnosed and undiagnosed cases are identified, as well as random sampling of birth certificates for ascertaining potential POP participants will be retained.
- Potential ASD and DD children will be identified through sources serving or evaluating children with developmental problems; sources for potential ASD and DD children may include, early intervention programs, special education programs, state autism registries, hospitals, and clinics. Final case status (i.e., confirmed cases) will be determined from an in person evaluation in which a qualified (and research-reliable) professional administers standardized developmental instruments to all children who either have a previous ASD diagnosis or who screen positive for potential ASD on an ASD screening instrument administered to all children's mothers during the initial (invitation) telephone call.
- Applicants are expected to demonstrate effective partnership with multiple data sources for potential ASD/DD participants and ability to sample from birth certificates to ensure a robust ascertainment pool.
- In SEED 3, applicants are also expected to develop a mechanism(s) to achieve response rate targets (see below). Active follow-up of non-responders is strongly encouraged. The exact mechanisms may vary across sites.
- Applicant must describe their study site in terms of both geography, size and sociodemographic characteristics. Each study site must be contiguous geographic sector defined by clear territory, state(s) or county(ies) boundaries. The corresponding birth population size in the area in 2014 should be a minimum of 40,000 births. The SEED 3 catchment area for applicants who are current SEED sites must include, but may not be limited to, entire SEED 2 study catchment area.

A focus of SEED 3 will be to increase response rates in order to better ensure the final sample is internally valid.

In order to obtain permissions for active follow-up (i.e., via phone calls and/or emails), SEED sites may need to focus more closely on selected sources for ASD and DD children. It will be acceptable to limit enrollment sources; however, sites must choose data sources that will allow enrollment of a study population that is diverse in terms of key demographics – race-ethnicity and socioeconomic status. Thus, even though cases will not be selected to be population-based, they will still include participants from key subgroups in the target population. (See complete protocol for further details).

- The SEED Phase 3 eligibility criteria will be the same as those in SEED 2. The only update is that eligible cohort birthdates for SEED Phase 3 child participants will be 2014-2017 (cohort dates subject to change depending on implementation considerations).

SEED 3 Data Collection

- The SEED 3 data collection protocol has been reduced in order to:
 - Continue to use the CIS-2 management system with minimal revisions/updates;
 - Ensure efficient harmonization of SEED 3 analytic data with the analytic data collected from the earlier SEED 1 and SEED 2 phases;
 - Eliminate some of the most time-intensive data collection instruments; and
 - Reduce processing and storage costs for the SEED Biorepository.
- All data collection instruments and examinations included in SEED 2 that will be retained in SEED 3 will be retained as is, without revision. This will allow for harmonization of SEED 3 data with data obtained from prior SEED phases.
- Data collection protocols in SEED 3 will be streamlined in comparison to SEED 2 such that several instruments will no longer be collected for children in any of the 3 study groups and several additional instruments will not be collected for children in 1 of the 3 study groups:
 - Pediatric care records will no longer be obtained and abstracted from any participants.
 - Neonatal care records will no longer be obtained and abstracted from any participants.
 - Children in the DD workflow -- defined as children recruited from "broad diagnostic net" sources who do not have a previous diagnosis of an ASD, are not being served under the autism public school special education eligibility category, and score below the a priori threshold (<11) on the autism screener used in SEED, the Social Communications Questionnaire (SCQ), will undergo a very curtailed protocol in SEED 3 compared to children in the ASD and POP workflows. The DD workflow protocol will no longer include: an in-person clinical assessment (Mullen and Vineland assessments; growth parameter measurements); other parent-administered developmental forms (Child Behavior Checklist [CBCL] and child Social Responsiveness Scale [SRS]), any bio-sample collection, any

medical record abstractions (including the aforementioned pediatric and neonatal care records and also the maternal prenatal care and labor and delivery records). Children will still be recruited into the DD group because this is an important source for ASD case finding, since many young children with ASDs are not diagnosed by 3-5 years of age. Also, the DD group will continue to be important in assessing recall bias for maternally reported risk factors and child health conditions. However, the full data collection protocol is no longer seen as necessary in SEED 3 because sufficient samples from the DD group were obtained in SEED 1 and SEED 2. (See complete protocol for further details).

- Blood specimens will still be obtained from both mothers and children in the ASD and POP workflows. However, the amount of blood collected will be reduced in SEED 3. The focus will be on ensuring there are have sufficient biosamples for genetic analyses – specifically whole genome sequencing and methylation assays -- of children and mothers included in the ASD and POP workflows. NOTE: saliva samples will be collected from all children and their mothers and fathers in the ASD and POP workflows
- Specific data collection instruments that will continue to be included in SEED 3 are the following:
 - Social Communication Questionnaire (SCQ) -- an ASD screening instrument administered via phone (estimated time 10-15 minutes);
 - Maternal telephone-assisted interview – includes questions on maternal reproductive history, pregnancy health and occupational history, and family demographics (estimated time 60 minutes);
 - Saliva specimens (ASD and POP workflows only -- child, biological mother, and if available biological father);
 - Blood specimens (ASD and POP workflows only -- child and biological mother); and
 - Clinical developmental evaluation (ASD and POP workflows only), including administration of:
 - **ASD workflow participants:**
 - Autism Diagnostic Observation Schedule (ADOS) – standardized child developmental assessment (estimated time 40 minutes);
 - Autism Diagnostic Interview-Revised (ADI-R) - standardized child developmental assessment based on parental interview (estimated time 90 minutes);
 - Vineland Adaptive Behavioral Scales (VABS) – parent-administered standardized interview assessing child cognitive and adaptive functioning (estimated time 40 minutes); and
 - Mullen Scales of Early Learning -- standardized child developmental assessment (estimated time 45 minutes).
 - **POP workflow participants:**
 - Mullen Scales of Early Learning (estimated time 45 minutes); and
 - Vineland Adaptive Behavioral Scales (VABS) – ONLY in instances of low Mullen scores (estimated time 40 minutes).
 - Self/parent-administered forms including:
 - Maternal medical history form -- two-page checklist type form (estimated time 10 minutes);
 - Paternal medical and occupational history form -- two-page checklist type form (estimated time 10 minutes);
 - Child health history form – four page form includes medical conditions checklist, brief sections on both gastrointestinal and sleep problems, and brief section on health insurance and medical home (estimated time 20 minutes);
 - Child Behavior Check List (ASD and POP workflows only) – standardized two-page checklist type form (estimated time 20 minutes);
 - Social Responsiveness Scale (child only) (ASD and POP workflows only) – standardized checklist type form (estimated time 20 minutes); and
 - Services and Treatment Questionnaire (ASD workflow only) – four-page form on index child treatments (estimated time 10 minutes).
 - Abstraction of prenatal and labor and delivery medical records (ASD and POP workflows only).

Component B: Biorepository

The objectives of Component B of this FOA are to support the maintenance and storage of the SEED Phase 1 and Phase 2 biosample repository and support the collection and storage of the SEED Phase 3 biosamples. It is CDC's goal that all SEED biosamples (from Phases 1, 2, and 3) will be stored in one repository.

Applicants under this FOA should describe how they will support the SEED 1 and SEED 2 biosample maintenance and the SEED 3 biosample protocol. Specifically, the Central Laboratory and Biosample Repository (CLBR) will be responsible for developing, implementing, and coordinating protocols for local site specimen collection and shipping of blood and saliva specimens to the CLBR (Phase 3 specimens); CLBR intake and processing of received specimens (Phase 3 specimens); acquisition and long term storage of specimens (Phases 1 and 2 specimens); and subsequent shipping of samples to other laboratories for analyses needed.

In SEED 1 both buccal and blood samples were collected from children and their biologic mothers and fathers in all three workflows when available. In SEED 2 both saliva and blood samples were collected from children and their mothers in all three

workflows and saliva samples were collected from fathers when available. In SEED 3 saliva and blood specimens will be collected, however, the SEED 3 laboratory protocol will be scaled back. Therefore, the number of families for whom biosamples will be collected will be reduced. Additionally, the amount of blood collected from mothers and children will be reduced and laboratory processing will also be reduced with a more streamlined protocol for collecting and processing specimens specifically needed for 1) whole genome sequencing from mothers' and children's samples; 2) methylation assays of children's samples; and 3) RNA assays of children's samples.

In SEED 1 and SEED 2 the following blood samples were collected:

- EDTA tubes (mothers + children),
- Serum separator tubes (SST) (mothers + children),
- PAXgene Blood RNA tubes (children only),
- Acid Citrate Dextrose (ACD) (mothers + children),
- CPT™ Cell Preparation tubes (mothers + children), and
- Guthrie blood spot cards (children only),

From these specimens, the following aliquots were frozen:

- PAXgene samples,
- Buffy coat,
- Plasma,
- Serum
- Cell pellets,
- Peripheral blood mononuclear cells (PBMC),
- Red blood cells (RBC),
- White blood cells (WBC),
- DNA (from buccal, saliva, buffy coat, and/or WBC),
- RNA derived from PAXgene tubes, and
- Dried blood Spots (DBS).

There will be an estimated 200,000 aliquots in long term storage from SEED Phases 1 and 2.

In SEED 3, lab costs will be reduced by 1) including only 5 sites (rather than 6 sites in SEED 2); 2) collecting bio-specimens from children and parents in the ASD and POP workflows only (i.e., bio-specimens collection from DD workflow families will be eliminated) and 3) collecting more limited blood samples from mothers and children. NOTE: Saliva specimens will continue to be collected from children and both parents in the ASD and POP workflows in SEED 3.

Specifically, in SEED 3 the following blood samples will be collected:

- EDTA tubes (mothers + children),
- Serum separator tubes (SST) (children only),
- PAXgene Blood RNA tubes (children only), and
- Guthrie blood spot cards (mothers + children).

From these specimens, the following aliquots are frozen:

- PAXgene samples,
- Buffy coat,
- White blood cells (WBC),
- DNA (from saliva, buffy coat, and/or WBC),
- RNA derived from PAXgene tubes, and
- Dried blood spots (DBS).

The reduction to 5 sites will result in an estimated 15-20% reduction in the number of families for whom biosamples will be collected. Eliminating the DD workflow families from bio-sample collection is estimated to result in a further 20% reduction in the number of families for whom bio-samples will be collected. Limiting the amount of blood collected from mothers and children is estimated to result in a 32% reduction in laboratory costs for sample processing and storage for those families for whom bio-samples will be collected.

Based on data from SEED 2 it is estimated that ~ 950 children will be included in the ASD workflow AND will participate in the in person clinic visit in SEED 3 (note – not all of these will become final ASD cases, but all will be eligible for bio-specimen collection if their mothers consent). It is further estimated that bio- samples will be collected from the ASD workflow families as follows:

- 80% mothers will provide saliva specimens,
- 80% mothers will provide blood specimens,

- 80% children will provide saliva specimens,
- 60% children will provide blood specimens, and
- 50% fathers will provide saliva specimens.

Based on data from SEED 2 it is estimated that ~600 children will be included in the POP workflow AND will participate in the in person clinic visit in SEED 3. It is further estimated that bio-specimens will be collected from the POP workflow families as follows:

- 80% mothers will provide saliva specimens,
- 80% mothers will provide blood specimens,
- 90% children will provide saliva specimens,
- 60% children will provide blood specimens, and
- 50% fathers will provide saliva specimens.

Component C: SEED 1 Follow-up Study

The objective of Component C of this FOA is to support the development and implementation of a study protocol and feasibility assessment for a follow-up study of children who enrolled in SEED 1 and completed the data collection protocol.

New sites must develop and submit agreements with one or more former SEED 1 sites to fully access all data needed to successfully conduct the follow-up study. Former SEED 1 sites may also propose follow-up of SEED 1 participants from other sites (in addition to their own) to maximize the sample size for this study. If former sites propose working with other SEED 1 sites, they must also develop and submit agreements documenting full data access.

The sites funded for this activity will work with GA SEED and CDC to develop a brief protocol. This protocol needs to include a plan to assess and report on the success of the follow-up study and the feasibility of implementing the protocol on a larger scale.

Sites will collectively develop the protocol and data collection activities within the parameters outlined below. These parameters are set to ensure timeliness, contain costs, and to ensure that this study is focused on CDC's population public health mission.

At each site, all children enrolled in SEED 1 who completed key components of data collection (maternal interview and clinic visit at a minimum) AND whose mothers consented to be contacted for future studies will be considered for inclusion in the SEED 1 follow-up study.

While in depth subgroup studies might be of interest scientifically, the primary objectives of this research effort will be to:

- Understand the long term health, functioning, educational achievement, and support needed among children identified at young ages as having ASD in comparison to children identified as having other DDs and children from the general population.
- Understand the developmental trajectory of children identified at young ages as having ASD.
- Establish a mechanism to maintain contact for future follow-up studies of the cohort as children begin the transition to adulthood.
- Re-consent participants to enable data sharing of biosample and genetic information collected and analyzed as part of SEED-1 with other federal agencies and research consortia. Note: SEED 1 consent forms did not include specific language for sharing SEED 1 participant data with genetic biorepositories. As IRB and other guidance has evolved since SEED 1 on the potential identifiability of genetic data, CDC would like to obtain new informed consents from SEED 1 participants before sharing any genetic data with external biorepositories. These consents will specifically detail what genetic and other data will be shared, describe the genetic autism biorepositories at NIH including who will have access to the data, and delineate both benefits and potential risks associated with genetic data sharing.

In order to maximize inclusion of all children (including those who have moved out of the study area since completion of the SEED 1 protocol) and to contain costs, data collection will be limited to instruments that can be administered via phone by interviewers and/or self/parent-administered via mailings or internet surveys.

Because this is the first funding cycle for a SEED follow-up study, a secondary objective of Component C is to assess the feasibility of SEED follow-up studies more generally. Sites will collaboratively develop a feasibility assessment and report of the activities conducted as part of the SEED 1 follow-up study. This assessment will include:

- Assessment of the feasibility of locating SEED 1 participants and recruiting them to participate in a follow-up study (with the eventual goal of implementing this on a larger scale).
- Experiences with implementation of a brief data collection protocol once the participant is contacted (such as a telephone interview at contact)
- Experiences with implementation of a protocol to re-consent participants for genetic data sharing.
- Development of a feasibility report. This report will describe the success of the study, including the response and completion rates, number of children contacted and included in the follow-up study, positive and negative experiences with data collection instrument(s), success in obtaining new informed consents for genetic data sharing, lessons learned, and

recommendations about whether and how to expand the follow-up protocol.

Suggested Timeline:

Year 1

Protocol will be developed

Approvals will be obtained

Years 2 through 5

Protocol will be implemented

A feasibility report will be collaboratively prepared by the CDC and Awardees.

Target Population

Component A: CADDRE SEED Phase 3

The SEED 3 target population includes children born in 2014-2017 to mothers residing in the geographic catchment areas of each of the SEED sites at the time of the child's birth, who also currently reside with their biological mothers within the SEED catchment area at the time of study enrollment.

Component B: Biorepository

N/A

Component C: SEED 1 Follow-up Study

The SEED 1 follow-up study target population is SEED 1 participants who completed the core SEED data collection protocol. Applicants are expected to work collaboratively with CDC and the SEED Data Coordinating Center in designing and implementing this follow-up protocol.

Collaboration/Partnerships

Component A: CADDRE SEED Phase 3

Established CADDRE SEED collaborative processes will be retained in SEED Phase 3. Workgroups with representatives from each site and CDC will be charged to provide guidance and oversight over all aspects of SEED Phase 3 implementation. In addition, the PI Workgroup (including all grantee and CDC PIs) and Data Sharing Committee will be responsible for making collaborative key decisions regarding SEED scientific and analytic issues and SEED publications or other external communication. The existing detailed CADDRE Data Analysis and Publications Guidelines will also continue to be used in order to:

1. Assure and expedite orderly and timely presentation to the scientific community of all pertinent data resulting from CADDRE SEED;
2. Promote accurate and scientifically sound presentations and papers from CADDRE and its collaborating investigators;
3. Promote collaboration among CADDRE sites and ensure that all participating investigators have the opportunity to be involved in data analysis and the preparation of CADDRE papers and presentations;
4. Assure that press releases, presentations, and publications related to SEED are accurate and objective, and do not compromise the collaborative study and the acceptance of its results;
5. Establish guidelines for authorship, acknowledgments, and funding citations for any presentations and publications of CADDRE; and
6. Maintain a record of proposed and published papers and presentations from CADDRE SEED.

Applicants are expected to work collaboratively with CDC to establish appropriate analytic methods to address data issues related to participant selection and response.

Applicants are expected to demonstrate willingness and ability to establish a written Memorandum of Understanding with the CADDRE Data Coordinating Center (DCC) outlining DCC- and site-specific roles and responsibilities in maintaining the confidentiality and security of the personally identifiable information collected as part of SEED.

Applicants must provide a statement of their willingness and ability to support SEED's data management, analysis and reporting plan:

- 1) Each site must use and support proper functioning of the centralized web-based CADDRE Information System.
- 2) Each site must contribute site-specific data to the SEED pooled dataset.
- 3) Each site must follow the CDC-approved mechanism for access and use of SEED analytic files, which will ensure that all CDC-required data security standards are maintained. (The currently approved mode for data access is via a remote data access server [RDA] maintained by the CADDRE DCC.)

- 4) Each site must be willing to implement procedures for contribution of site SEED Phase 3 genetic data to National Database for Autism Research (NDAR) and the Database for Genotypes and Phenotypes (dbGaP) at the end of the project.
- 5) Each site must adhere to CADDRE Data Sharing and Publication Guidelines for analysis, presentation, publication, and data release. The Guidelines promote and prioritize analyses using the SEED pooled data set (data from all 5 sites) above analyses based on single site data. These guidelines also include CDC specific scientific requirements pertaining to CDC clearance of manuscripts and abstracts.

Component B: Biorepository

Established CADDRE SEED collaborative processes will be retained in SEED Phase 3. CDC will work closely with the Central Laboratory and Biosample Repository (CLBR) and facilitate and coordinate activities and communications between the CLBR and the CADDRE Network and CLBR and the SEED Data Coordinating Center. The SEED Biomonitoring Committee will also be maintained to assess all analytic proposals that includes analyses of SEED biosamples, to ensure that the CADDRE network is intentional in how this limited resource is used.

Applicants must provide a statement of their willingness and ability to support SEED's data management, analysis and reporting plan:

- 1) Must use and support proper functioning of the centralized web-based CADDRE Information System.
- 2) Must support established CADDRE/SEED procedures for tracking biosamples while maintaining confidentiality.

Component C: SEED 1 Follow-up Study

Collaborative processes and workgroups similar to those established for the core SEED project will be developed for the SEED 1 study. The existing detailed CADDRE Data Analysis and Publications Guidelines will also serve as a guide for any publications or presentations from any SEED 1 follow-up study.

Applicants are expected to demonstrate willingness and ability to establish a written Memorandum of Understanding with the CADDRE Data Coordinating Center (DCC) outlining DCC- and site-specific roles and responsibilities in maintaining the confidentiality and security of the personally identifiable information collected as part of SEED.

All applicants, including both new sites, and former SEED 1 sites are encouraged to apply for this component. New sites must develop and submit agreements with one or more former SEED 1 sites to fully access all data needed to successfully conduct the follow-up study. Former SEED 1 sites may also propose follow-up of SEED 1 participants from other sites (in addition to their own) to maximize the sample size for this study. If former sites propose working with other SEED 1 sites, they must also develop and submit agreements documenting full data access.

Applicants must provide a statement of their willingness and ability to support SEED's data management, analysis and reporting plan:

- 1) Each site must use and support proper functioning of the centralized web-based CADDRE Information System.
- 2) Each site must contribute site-specific data to the SEED 1 Follow-up Study pooled dataset.
- 3) Each site must follow the CDC-approved mechanism for access and use of SEED analytic files, which will ensure that all CDC-required data security standards are maintained. (The currently approved mode for data access is via a remote data access server [RDA] maintained by the CADDRE DCC.)
- 4) Each site must adhere to SEED 1 Follow-up Study Data Sharing and Publication Guidelines for analysis, presentation, publication, and data release. SEED 1 Follow-up Study Data sharing and publication guidelines are still to be developed but will be consistent with existing CADDRE Data sharing and publication guidelines.

Evaluation/Performance Measurement

Component A: CADDRE SEED Phase 3

The a priori SEED 3 enrollment and completion targets are as follows:

- Each site is expected to contribute 125 participants into each of the 3 study groups (ASD, DD, and POP) who have both enrolled and completed the study protocol.
- In addition to enrollment and completion numbers, minimum *response rate* targets for SEED 3 are:
 - 50% for children invited from clinical and school data sources who are identified as having a previous ASD diagnosis or autism special education eligibility classification;
 - 40% for children invited from clinical and school data sources who are NOT identified as having a previous ASD diagnosis or autism special education eligibility classification (some of these children will become ASD cases and some will be included in the DD comparison group);
 - 30% for children identified from birth certificate random sampling for the POP group. **Note:** response rates are calculated as # children enrolled / # children invited – (# children known to be ineligible + # children not contacted but

estimated to be ineligible). This is the same definition for response rate used in SEED 1 and SEED 2.

Eligibility will be determined by an eligibility screener administered during first phone contact. For children never contacted, eligibility is estimated by assuming the ineligible rate among those never contacted is the same as the ineligible rate among those who were contacted.

- Minimum study completion rates targets for SEED 3 are:
 - 70% in all three study groups.

Completion rates are calculated as # children who completed study protocol / # children enrolled.

Completion of study protocol includes completion of most study instruments. The PIs in SEED 1 and SEED 2 collectively developed a study completion definition. Similar definitions will be adapted for SEED 3 by the site PIs.

Component B: Biorepository

Applicants are expected to perform quality assurance and quality control measures on sample processing, tracking, and biosample storage. Review of these measures will require submission of quarterly sample processing reports including justification of sample processing backlogs, monthly biorepository inventory reports, and annual updates of SEED lab protocol manual.

Component C: SEED 1 Follow-up Study

The a priori SEED 1 follow-up phase 1 study recruitment enrollment and completion targets are as follows:

- Each site is expected to:
 - Successfully trace and contact a minimum of 60% of SEED 1 participants deemed eligible for inclusion in the follow-up study (final eligibility criteria will be decided upon collaboratively during protocol development).
 - Enroll a minimum of 70% of eligible SEED 1 participants who are successfully contacted.
 - Complete data collection activities on 90% of enrolled participants.
 - Obtain new consents for genetic data sharing from 70% of enrolled participants.

One of the goals of the follow-up study is to determine the feasibility of implementing this protocol; thus, recruitment enrollment and completion targets may be revised by CDC if needed.

Translation Plan

Component A and B.

Applicants are expected to present the findings from research analyses at both scientific and community partner meetings and publish in peer-reviewed journals. The CADDRE Network SEED Data Sharing Committee will continue to set guidelines for use of the SEED data and publication of research findings. CDC priorities will also be considered in setting research priorities; this primarily entails ensuring that initial work on priority analyses are based on public health importance (including consideration of the potential strength of association, risk factor prevalence, biologic plausibility, preventability, etc.). Study participants will be kept informed of study progress and results through biannual SEED newsletters.

Component C: Follow-up Study

Applicants are expected to collaborate with CDC and other grantees on the development of a follow-up study feasibility report and other scientific presentations and publications detailing study findings. Study participants will be kept informed of study progress and results through biannual SEED newsletters.

Component A, B and C.

Applicants are expected to include a plan on sharing research resources and data. This should include:

- Use and support of the centralized web-based CADDRE Information System for data entry.
- Contribution of site-specific data to the SEED pooled dataset, which will be maintained and or overseen by CDC through their approved mechanism (maintained by the CADDRE DCC.)
- Use of the CDC-approved mechanism for access and use of SEED analytic files, which will ensure that all CDC-required data security standards are maintained. (The currently approved mode for data access is via a remote data access server [RDA] maintained by the CADDRE DCC.)

OMB/PRA may apply.

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: \$21,600,000

Component A (SEED-3): The estimated total funding (direct and indirect) for the first budget period, (07/01/2016 – 06/30/2017), is \$3,200,000. The estimated total funding (direct and indirect) for the entire 5-year project period, (07/01/2016 – 06/30/2021), is \$17,600,000. Estimated Number of Awards: up to 4. Average amount of each award: YR 1: \$800,000 YRS 2-5: \$900,000.

Component B (Biorepository for SEED-3): The estimated total funding (direct and indirect) for the first budget period, (07/01/2016 – 06/30/2017), is \$300,000. The estimated total funding (direct and indirect) for the entire 5-year project period, (07/01/2016 – 06/30/2021), is \$1,500,000. Estimated Number of Awards: 1. Average amount of each award: YRS 1-5: \$300,000.

Component C (Follow-up Study): The estimated total funding (direct and indirect) for the first budget period, (07/01/2016 – 06/30/2017), is \$500,000. The estimated total funding (direct and indirect) for the entire 5-year project period, (07/01/2016 – 06/30/2021), is \$2,500,000. Estimated Number of Awards: up to 2. Average amount of each award: YRS 1-5: \$250,000

Anticipated Number of Awards: 7

The estimated total level of funding (direct and indirect for entire project period in dollars) that is available for the FOA is \$21,600,000 to support up to 7 anticipated awards (over the 3 components). Awards issued under this FOA are contingent upon availability of funds and a sufficient number of meritorious applications. Because the nature and scope of the proposed research will vary from application to application, it is also anticipated that the size of each award may also vary. The total amount awarded and the number of awards will depend upon the number, quality and cost of the applications received.

The estimated total funding (direct and indirect) for the first budget period, (07/01/2016 – 06/30/2017), is \$4,000,000. The estimated total funding (direct and indirect) for the entire project period, (07/01/2016 – 06/30/2021), is \$21,600,000.

Component A: CADDRE SEED Phase 3

\$800,000 (total direct and indirect costs); This ceiling is for the first 12 month project period.

Floor \$0 (total direct and indirect costs)

Component B: Biorepository SEED 3

\$300,000 (total direct and indirect costs); This ceiling is for the first 12 month project period.

Floor \$0 (total direct and indirect costs)

Component C: SEED 1 Follow-up Study

\$250,000 (total direct and indirect costs); This ceiling is for the first 12 month project period.

Floor \$0 (total direct and indirect costs)

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

Award Ceiling: \$800,000 Per Budget Period

Award Floor: \$0 Per Budget Period

Total Project Period Length: 5 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

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

Additional Eligibility Category:

2. Foreign Organizations

Foreign Organizations are not eligible to apply.

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

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

3. Special Eligibility Requirements

Applicants must provide the following in Appendix A of the application:

1. 2014 vital statistics data on number of births for all state territories, counties, etc included in the site study catchment area and a map of the study catchment area.
2. Data that describes the racial/ethnic/socioeconomic characteristics of the proposed study catchment area and study population (e.g., from official reports, documents, websites).
3. Evidence of negotiation with state vital records holder concerning applicant's terms of access to birth certificate data (e.g., letter on official letterhead, MOU, or other official documentation)
4. Evidence of negotiation (e.g., letter on official letterhead, MOU, or other official documentation) of established partnerships with ASD/DD ascertainment source(s) (might be clinics, healthcare providers, school systems, state disability centers, etc.).

Provide documentation in Appendix A with appropriate labels indicating to which criterion above (1 through 4) the documentation pertains.

If your application is incomplete or non-responsive to the special eligibility requirements listed in this section, it will not enter into the review process.

4. Justification for Less than Maximum Competition

N/A

5. Responsiveness

Evidence of special eligibility criteria listed in number 3 above must be presented in Appendix A of the application. If your application is incomplete or non-responsive to these requirements, it will not enter into the review process.

Component A: CADDRE SEED Phase 3

The budget for the application's Year 1 does not exceed the ceiling amount of \$800,000

Component B: Biorepository

The budget for the application's Year 1 does not exceed the ceiling amount of \$300,000.

Component C: SEED 1 Follow-Up Study

The budget for the application's Year 1 does not exceed the ceiling amount of \$250,000

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

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

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

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

All applicant organizations **must obtain** a DUN and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number is a nine-digit number assigned by Dun and Bradstreet Information Services. An AOR should be consulted to determine the appropriate number. If the organization does not have a DUNS number, an AOR should complete the [US D&B D-U-N-S Number Request Web Form](#) or contact Dun and Bradstreet by telephone directly at 1-866-705-5711 (toll-free) to obtain one. A DUNS number will be provided immediately by telephone at no charge. Note this is an organizational number. Individual Program Directors/Principal Investigators do not need to register for a DUNS number.

Additionally, all applicant organizations must register in the **System for Award Management (SAM)**. Organizations must maintain the registration with current information at all times during which it has an application under consideration for funding by CDC and, if an award is made, until a final financial report is submitted or the final payment is received, whichever is later. SAM is the primary registrant database for the Federal government and is the repository into which an entity must provide information required for the conduct of business as a recipient. Additional information about registration procedures may be found at the SAM internet site at <https://www.sam.gov/index.html>.

If an award is granted, the 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.

Only one application per institution (normally identified by having a unique DUNS number) is allowed.

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 (TIMS) staff at (770) 488-2700 or pgotim@cdc.gov for further instructions. Hours: Monday - Friday, 7am – 4:30pm U.S. Eastern Time. CDC Telecommunications for the hearing impaired or disabled is available at: TTY 1-888-232-6348.

2. Content and Form of Application Submission

It is critical that applicants follow the instructions in the SF424 (R&R) Application Guide (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. These forms can be downloaded from <http://grants.nih.gov/grants/forms.htm>

3. Letter of Intent

Due Date for Letter of Intent: **01/04/2016**

Is a LOI: Recommended but not Required

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

Component name applying for

The letter of intent should be sent to:

Michael A. Brown, M.P.H.

Scientific Program Official

Extramural Research Program Operations and Services

Centers for Disease Control and Prevention
4770 Buford Hwy, NE
Mailstop F-80
Atlanta, GA 30342
Telephone: (770) 488-5118
E-mail: mab5@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

Applicants must submit a separate research plan for each Component of funding. Applicants should clearly indicate the Component for which they are applying and should include at the beginning of the title, the respective Component under which research plan should be considered (i.e., Component A, Component B, or Component C).

Please note: the page limitations specified for this application, under Section IV number 7: i.e. no more than 25 pages for Research Strategy and 50 pages for appendices, are per component.

For each Component, the applicant's research plan should address activities that will be conducted over the entire project period and should include the following items:

Component A: CADDRE SEED Phase 3

- 1) Describe your experience in implementing studies in population-based autism surveillance or epidemiologic research that are relevant to your ability to successfully implement SEED Phase 3 and support SEED Phase 3 scientific goals. Please include:
 - a) Descriptions of scope, complexity and size (including final sample size) of previous studies;
 - b) Descriptions of measures of implementation success from previous studies (e.g., research recruitment rates; ASD surveillance rates in line with other published estimates; quality control (QC) measures; estimates of data collection completeness on each enrolled participant or surveillance case; representativeness and/or generalizability of research or surveillance sample and results; timeliness of study implementation);
 - c) Professional reports, publications and presentations; and
 - d) Descriptions of relevance to autism surveillance or research needs of previous studies (i.e., significance of knowledge gaps that were filled).
- 2) Describe your autism research capacity as demonstrated by staff expertise and publication record.
- 3) Describe your study catchment area (must be a contiguous geographic sector defined by clear territory, state(s) or county(ies) boundaries) and the corresponding birth population size in the area in 2014 (minimum of 40,000 births). If you are a former SEED site, describe the overlap between the SEED Phase 2 catchment area and the proposed SEED Phase 3 catchment area.
 - a) Describe the race/ethnicity and sociodemographic characteristics of your proposed catchment area study population.
- 4) Describe your ability to access multiple data sources for CASE/DD ascertainment.
 - a) Both health and education ascertainment sources for potential CASE and DD participants is ideal;
 - b) Provide documentation demonstrating partnership with multiple CASE/DD ascertainment sources that:
 - i) Collectively serve a substantial proportion of the preschool ASD population in the proposed site study catchment area (provision of an estimate of that proportion in the application is desirable); and
 - ii) Serve or include children who are 24-68 months of age, including children who would fall within the SEED Phase 3 birth cohort: July 1, 2014- June 30, 2017
 - c) Demonstrated track record of multiple source collaboration for ascertainment for autism surveillance or research purposes.
 - d) Describe your access to birth certificate files. Applicants must have access to birth certificate files for: 1) identifying and contacting potential invited participants (population control group); 2) verifying study eligibility, i.e., birth residence requirements (all study groups of enrolled participants); and 3) compiling birth certificate data on all children who enroll in SEED 3 for use in various risk factor analyses. It is also desirable that applicants have access to birth certificate files for all invited participants to characterize respondents and non-respondents.
 - e) Provide documentation demonstrating access (include any provisions to access) to birth certificate files for:
 - i) selecting and contacting potential participants (this capability is required, although means of access and by whom may vary);
 - ii) linking birth certificate data to enrolled participants ascertained from education and clinic sources to confirm study birth residence eligibility requirements (this capability is required, although means of linkage and by whom may vary);
 - iii) collecting birth certificate data on all enrolled participants for SEED analyses (describe any access restrictions to specific types of birth certificate data for enrolled participants); and
 - iv) using birth certificate data to characterize the broader study population.
 - v) Describe mechanism to allow for linkage of limited birth certificate data on all participants (ASD, DD, and POP groups) invited in SEED 3 including those who are never successfully contacted, those who refuse contact, and those contacted but found to be ineligible, such that SEED investigators will be able to directly assess characteristics of respondents vs. non-respondents.

Birth certificate data of interest include key socio-demographic factors – child sex, maternal race-ethnicity, maternal age at birth, maternal education at birth. While individual-level data is preferred, aggregate data with distributions of aforementioned key variables will also be helpful in assessing potential response bias.
- 5) Provide a detailed description of your site-specific plan for implementing SEED Phase 3 ascertainment, recruitment and data collection procedures:
 - a) Describe specific methods to implement SEED Phase 3 in order to:
 - i) Recruit, at a minimum, approximately 540 participants (approximately 180 per participant group) per site and

achieve, at a minimum, complete data collection on 375 participants (a minimum of 125 participants in each of the three study groups) per site. Evidence of this ability should include demonstration of a high quality implementation infrastructure.

ii) Achieve response rate of: 50% for children identified from education and clinical sources as potential ASD cases; 40% for children identified from education and clinic sources as having other DDs; and 30% for children identified from the POP group through random sampling of the birth certificate files.

b) Describe your specific plan for achieving target response rates as outlined above. Describe methods to recruit SEED participants including all approaches to maximize recruitment rates. Active follow-up of invited participants who do not respond to the initial invitation mailing is strongly encouraged. Applicants should provide evidence of current negotiation with each data source concerning the recruitment procedures. Strategies to maximize response might include but are not limited to:

- i) Community outreach, including social networking, to boost awareness and interest among invitees;
- ii) Strategies to facilitate invitee response to the study invitation letter by providing multiple response mode options (e.g., text messaging, logging into a web site, mail-in response card, directly calling a dedicated study telephone number);
- iii) Robust tracing of contact information using multiple people search data bases and social networking sites; and
- iv) Dedicated staff supported by the project to implement such recruitment strategies, including persons to work closely with data sources in order to optimize response to invitations and possibly provide active post-invitation follow-up.

6) Describe your ability to evaluate research.

a) Applicant must demonstrate willingness and ability to carry out within- and between-site SEED QC to maintain a priori CADDRE SEED standards for implementation and data collection procedures and developmental assessment reliability.

7) For QC purposes, willingness and ability to video-tape developmental assessments and audio-record recruitment/interview telephone calls (for the latter, only temporary storage of audio-recorded telephone calls is required until QC is complete). Describe your ability to deal with data security and confidentiality:

- a) Approach for maintaining confidentiality and privacy of all participants; and
- b) Willingness and ability to establish a written Memorandum of Understanding with the CADDRE Data Coordinating Center (DCC) outlining DCC- and site-specific roles and responsibilities in maintaining the confidentiality and security of the personally identifiable information collected as part of SEED.

8) Describe your ability and willingness to support the SEED data management, analysis and reporting plans:

- a) Awardee must be able to use and support site-specific proper functioning of the centralized web-based CADDRE Information System created and managed by the DCC
- b) Ability to conduct site-specific data cleaning tasks in a timely manner, including tasks related to preparation of analytic data;
- c) Awardee must contribute all site-specific SEED data to the SEED pooled dataset;
- d) Awardee must plan to implement procedures (e.g., specific participant consent) for contribution of SEED Phase 3 data to the National Database for Autism Research (NDAR) at the end of the project; and
- e) Awardee must adhere to the existing CADDRE Data Sharing and Publication Guidelines for analysis, presentation, publication, and data release.

9) It is expected that a minimum of 5 manuscripts will be developed by each applicant. The CDC with guidance from the CADDRE data sharing committee will determine access and publication policies.

10) Describe your willingness and ability to assume active participation and take leadership roles in CADDRE committees/workgroups, conference calls, and in-person meetings.

11) Describe your Education and Outreach Plan:

- a) Describe a community and potential participant outreach plan to enhance recruitment, retention, and participant satisfaction; and
- b) Provide a plan for communication with study participants, data sources, and the local community regarding study progress and results (in addition to the established practice of sending SEED newsletters twice a year).

12) Describe your Staffing Plan:

- a) Provide a clear management and staffing plan to support all SEED Phase 3 activities.
- b) Minimum personnel should include: PI; project coordinator; epidemiologist (if not the PI; at least 20% effort); person(s) dedicated to enhancing recruitment, e.g., community outreach, working with sources to optimize contact and recruitment (at

least the equivalent of 1 person at 100% effort); recruiter/interviewers; medical record abstractors; developmental clinicians; phlebotomist; data entry/cleaning staff.

13) Describe your Facilities:

- a) Evidence that applicant has appropriate facilities to support all SEED Phase 3 activities and hard copy storage needs (e.g., hard copies of self-administered forms and questionnaires, medical records).
- b) Evidence for access to clinical space with sufficient availability to support the expected SEED Phase 3 participant volume and flexible and timely scheduling of the developmental assessment and phlebotomy, or a feasible non-clinical alternative (e.g., for the latter, demonstration of ability to successfully conduct home data collection visits including phlebotomy).

14) Provide a detailed budget and line-item justification of all operating expenses that are consistent with the planned activities of the project. Include:

- a) Recruitment support costs, apart from personnel, e.g., community outreach, public media, social networking, invitee response options;
- b) Travel support:
 - i) Proposed budget to include funds for at least 2 persons to attend an annual CADDRE in-person meeting in Atlanta.
- c) Equipment
 - i) Developmental assessment forms and materials, video camera, venous blood collection supplies (excluding blood tubes that are provided by the CLBR), laptops/encrypted thumb drives/software and related IT needs
- d) Miscellaneous
 - i) Recruitment costs (tracing, mailing)
 - ii) Participant mailings and incentives
 - iii) Biologics shipping
 - iv) Record retrieval and on-site storage costs

Component B: Biorepository

1) Describe your experience and ability to successfully serve as the SEED Central Laboratory and Biosample Repository and support SEED scientific goals, including support of saliva sample and blood specimen collection, processing and storage for SEED Phase 3 and storage of SEED Phase 1 and SEED Phase 2 specimens. Please include:

- a) Descriptions of scope, complexity and size of previous biorepository activities such as:
 - i) total sample size of processed and/or archived specimens
 - ii) diversity of specimen types that were handled
 - iii) diversity of laboratory processes applied to received specimens
- b) Measures of implementation success from previous biorepository activities, such as: success in support of local site specimen collection activities; work flow rates for samples received and processed within a set period to assess efficiency of laboratory operations; QC measures; development and/or refinement of laboratory techniques, including DNA extraction from saliva samples, to support scientific goals of study; capability of maintaining a current tracking record of specimens and providing accurate and timely specimen inventory reports; timeliness of all laboratory support processes.
- c) Professional reports, publications and presentations

2) Describe your capacity to support SEED biorepository needs as demonstrated by staff expertise

3) Describe plan for transport and storage of existing SEED 1 and SEED 2 specimens. The CLBR grantee will work with the CDC to facilitate access and responsibility for storage for SEED Phase 1, 2 and 3 specimens.

4) Describe a detailed site-specific plan for implementing SEED Central Laboratory and Biosample Repository procedures and provide evidence for your capability of handling SEED biosample collection volume and storage needs. Evidence of this ability should include demonstration of a high quality implementation infrastructure, including an accurate and timely biosample tracking system.

5) Describe your biosample tracking and storage standard operating procedures in case of catastrophic events

- 6) Describe your ability to evaluate research, specifically appropriate laboratory QC procedures by providing a detailed QC plan
- 7) Describe your ability and approach for maintaining confidentiality and privacy of all participant biosample data
- 8) Describe your ability and willingness to support the SEED biosample tracking and data management plans in collaboration with the CADDRE Data Coordinating Center.
- 9) Describe a clear management and staffing plan to support SEED Central Laboratory and Biosample Repository activities, including retrieval and shipment of archived specimens for analysis at other facilities, as needed
- 10) Describe your ability to provide appropriate facilities to support all SEED Central Laboratory and Biosample Repository activities and archival needs
- 11) Provide a detailed budget and line-item justification of all operating expenses that are consistent with the planned activities of the project. Include:
 - a) Travel support:
 - i) Include funds for at least 1 person to attend an annual CADDRE in-person meeting in Atlanta
 - b) Laboratory equipment and supplies, including specimen collection supplies (saliva collection kits, Guthrie cards, blood tubes, shipping containers) to be provided to SEED sites
 - c) Specimen processing costs
 - d) Specimen storage and retrieval costs
 - e) Miscellaneous, including biologics shipping costs when applicable

Component C: SEED 1 Follow-up Study

- 1) Describe your experience in implementing an epidemiologic follow-up study or epidemiologic research relevant to your ability to successfully plan and implement SEED Phase 1 follow-up study. Please include:
 - a) Descriptions of scope, complexity and size (including final sample size) of previous studies,
 - b) Descriptions of measures of implementation success from previous studies (e.g., research recruitment and enrollment rates; study completion rates).
 - i. Professional reports, publications and presentations, and
 - c) Descriptions of relevance to autism research (i.e., significance of knowledge gaps that were filled)
- 2) Describe your ability to access complete tracking data of SEED 1 participants from 1 or more SEED 1 sites
 - a) Demonstrate access to SEED 1 participants full contact information such as names and addresses of mother and child and names and addresses of any other contacts collected from participants during SEED 1.
 - b) Demonstrate access to full data from SEED 1 participants including: consent information (including whether participant consented to be contacted for future studies); study completion information (whether the participant completed key steps of the SEED 1 protocol such as clinic visit); and analytic data from all study instruments.
 - c) All new sites and all former CADDRE SEED sites who propose including participants from sites other than their own please describe access to SEED 1 participants including information on any negotiation and agreements with previous SEED sites to allow you to access the data needed to trace, recruit, and contact their SEED 1 participants.
 - i. NOTE: Access to SEED 1 data will be supported by the CADDRE/SEED Data Coordinating Center (DCC) (to be funded under a separate agreement). It is acceptable to develop an agreement whereby the applicant PI for this follow-up study and limited key personnel are added as investigators to another SEED 1 site's research protocol and thereby obtain rights to data access through DCC or directly from the SEED 1 site, provided all established SEED/CADDRE security and confidentiality procedures are followed.
 - ii. Provide evidence of agreement (e.g., letter or other official documentation) with any SEED 1 sites (besides your own) that you will include in this project. Any negotiation or agreement should include language describing permissions allowing you to: 1) access the data necessary to select SEED 1 participants for follow-up -based on their SEED 1 consents, SEED 1 workflow and final study group classification, and SEED 1 study steps and instruments completed; 2) access the data necessary to locate and follow-up those participants--i.e., by using all contact information provided by study families in SEED 1 as a starting point; and 3) access to all other SEED 1 analytic data files such that the original SEED 1 analytic data can be linked with any data generated through the follow-up project. This data access must occur using the established CADDRE data access mechanism--i.e., using

the current remote database access (RDA) system developed and maintained by the CADDRE DCC or any future mechanisms developed and/or approved by CDC for the CADDRE Network.

- 2) Describe the estimated sample of SEED 1 participants you are able to contact for potential inclusion in a follow-up study. Provide sample sizes of participants with a final SEED 1 classification of ASD, DD, and POP who have provided consent for future studies and who have completed most SEED 1 study steps (minimum SCQ, maternal (caregiver) interview; clinic visit (Mullen and if applicable Vineland, ADOS, and ADI-r). Note: as part of this cooperative agreement, the funded sites will work with the CDC to develop the final protocol for this follow-up study and feasibility assessment. Thus, the exact sample of children who will be included in the follow-up study is yet to be determined; however, the groups described above will be carefully considered for inclusion.
- 3) Describe the methods you will use to successfully implement active follow-up of SEED Phase 1 participants. Include description of your site's capacity to trace SEED 1 participants to obtain the most current residency and contact information and your site's ability recruit SEED 1 participants who are contacted. Describe procedures you would take to maximize participant contact (i.e., minimize loss to follow-up) and maximize participation once contacted.
- 4) Describe your ability to deal with data security and confidentiality
 - i) Approach for maintaining confidentiality and privacy of all participants
 - ii) Willingness and ability to establish a written Memorandum of Understanding with the CADDRE Data Coordinating Center (DCC) outlining DCC- and site-specific roles and responsibilities in maintaining the confidentiality and security of the personally identifiable information collected as part of SEED 1 Follow-up Study.
- 5) Describe your Staffing Plan:
 - i) Provide a clear management and staffing plan to support all SEED 1 follow-up study activities
 - ii) Minimum recommended staffing should include: PI; project coordinator (at least 20 percent effort); epidemiologist (if not the PI; at least 10% effort); study recruiter/interviewer; data entry/cleaning staff (it is possible that recruiter/interviewer staff might also perform data entry and cleaning activities).
 - iii) Provide a detailed budget and line-item justification of all operating expenses that are consistent with the planned activities of the project. Include:
 1. Recruitment support costs, apart from personnel, e.g., community outreach, public media, social networking, invitee response options
 2. Travel support:
 - i. proposed budget to include funds for at least 1 person to attend an annual CADDRE in-person meeting in Atlanta
 3. Equipment
 - i. Laptops/encrypted thumb drives/software and related IT needs
 4. Miscellaneous
 - i. Recruitment costs (tracing, mailing)
 - ii. Participant mailings and incentives

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.

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 50 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) (<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 TIMS at 770-488-2700; 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: **02/11/2016**

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

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

Funds will be restricted until:

- IRB and OMB/PRA (if needed) approvals are obtained.
- Human Subjects Education Requirement documentation is provided.

12. Other Submission Requirements and Information

Application Submission

Applications must be submitted electronically following the instructions described in the SF 424 (R&R) Application Guide.

PAPER APPLICATIONS WILL NOT BE ACCEPTED.

Applicants must complete all required registrations before the application due date. Section III.6 "Required Registrations" contains information about registration.

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

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

The applicant organization must ensure that the DUNS number it provides on the application is the same number used in the organization's profile in the eRA Commons and for the System for Award Management (SAM). Additional information may be found in the SF424 (R&R) Application Guide.

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

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

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

Section V. Application Review Information

1. Criteria

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

Overall Impact

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

b. 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?

Component A: CADDRE SEED Phase 3

Do the investigators have a successful track record in autism epidemiologic research? Have previous research results provided high quality outputs and contributed to improvements in public health practice and population health?

Has the applicant demonstrated the willingness and ability to assume active participation and take leadership roles in CADDRE committees/workgroups and meetings?

Component B: Biorepository

Is the applicant's past performance well suited to the project? Have they provided solid evidence for successful implementation of biosample repository activities for large research studies?

Has the applicant demonstrated willingness and ability to assume active participation in CADDRE committees/workgroups and meetings as needed?

Component C: SEED 1 Follow-up Study

Is the applicant's past performance well suited to the project? Have they provided solid evidence for successful implementation and completion of research studies, particularly studies involving longitudinal follow-up?

Has the applicant demonstrated the willingness and ability to assume active participation in the development of the study protocol that includes the CDC parameters described in the FOA and to actively participate in CADDRE committees/workgroups and meetings?

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?

Component A: CADDRE SEED Phase 3

Has the applicant demonstrated capacity in terms of size of birth population covered; coverage of data sources in the population; and methods for locating, and recruiting participants to achieve the minimum enrollment and completion targets of 125 participants with complete data collection in each of the final study groups – ASD, DD, and POP? Has the applicant demonstrated capacity in terms of recruitment methods to achieve the minimum response and completion rates as specified in the FOA?

Does the proposed CADDRE/SEED Phase 3 study catchment includes at least 40,000 births in 2014? And is the study catchment area in a contiguous geographic sector defined by clear territory, state(s) or county(ies) boundaries?

Does the applicant have access to multiple data sources for participant ascertainment that collectively serve a substantial proportion of the preschool autism population in the proposed study catchment area?

Has the applicant provided information on the number and types of sources they will be working with and an estimate of the proportion of the preschool autism population served by their sources? Has the applicant demonstrated that these sources serve diverse population subgroups in their catchment area?

Has the applicant provided evidence of their partnerships with the multiple ASD/DD data sources? Evidence may include

letters of support or other materials that document partnership with each ASD/DD ascertainment source and verify that the source serves or includes children in the SEED Phase 3 cohort.

Has the applicant provided evidence of negotiation with the holder of vital records concerning terms of access to birth certificate data? Has the applicant provided documentation to support access to birth certificate files for 1) identifying and contacting potential invited participants (population control group); 2) verifying study eligibility, i.e., birth residence requirements (all study groups of enrolled participants); and 3) compiling birth certificate data on all children who enroll in SEED 3 for use in various risk factor analyses. Evidence of negotiation (e.g., letter or other official documentation) with the state vital records holder should be provided concerning the applicant's terms of access to birth certificate data for these purposes.

Can the applicant also demonstrate access to birth certificate data, including data needed on key sociodemographic factors, for all invited participants (all three study groups – ASD, DD, and POP), in a manner that allows assessment of potential response bias by comparing the final enrolled SEED 3 sample to the total invited sample on the distributions of key sociodemographic characteristics?

Has the applicant demonstrated a high quality and innovative site-specific plan for robust recruitment, participant retention, and implementation of SEED Phase 3 data collection protocol, with a special emphasis on recruitment strategies as specified in the FOA? Do the recruitment strategies include dedicated staff working with sources to optimize contact and recruitment (at least the equivalent of 1 person at 100% effort) and means of support to enhance recruitment? Has the applicant provided evidence of negotiation with each data source concerning follow-up of non-responders to the study invitation?

Has the applicant provided a detailed staffing and resources plan, including a description of staff time commitments and necessary expertise of staff (currently available or to be identified) in critical areas of implementation (project coordination, recruitment, interviewing, clinical evaluation, phlebotomy, medical record abstraction, quality control)?

Has the applicant provided a high quality plan for participant outreach to enhance recruitment? Has the applicant provided a high quality plan for communication of study progress and results to the community, local partners, and participants?

Component B: Biorepository

Has the applicant demonstrated a high quality plan for implementing SEED Central Laboratory and Biosample Repository responsibilities and associated procedures?

Component C: SEED 1 Follow-up Study

Does the applicant have access to data from SEED 1 participants from one or more previous SEED sites necessary to conduct a follow-up study? Does the applicant demonstrate access to full data including contact information, consent information, SEED 1 study completion information, and analytic data from all SEED 1 study instruments?

If a new site or a former CADDRE/SEED site applicant proposing access to a different SEED 1 sites participant; does the applicant include evidence of negotiation (e.g., letter or other official documentation) with those SEED 1 sites? Does such evidence include specific language describing permissions allowing full access of the data needed?

Does the applicant adequately describe: the potential estimated sample of SEED 1 participants available for follow-up; the methods that will be used for active-follow-up of participants and the site's capacity to trace SEED 1 participants to maximize contact and to recruit SEED 1 participants in a manner that maximizes participation once contacted?

Has the applicant provided a detailed staffing and resources plan, including a description of staff time commitments and necessary expertise of staff (currently available or to be identified) in critical areas of implementation (project coordination, recruitment, and interviewing)?

Components A, B, and C

Has the applicant demonstrated the willingness and ability to carry out SEED quality control, data security protocols, and data management protocols? Has the applicant demonstrated willingness to adhere to CADDRE confidentiality, data sharing, and publication guidelines?

Has the applicant provided a data management, analysis, and reporting consistent with the FOA specifications?

Environment

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

Component A: CADDRE SEED Phase 3

Has the applicant adequately described the site's proposed study catchment area, birth population size in 2014, and population sociodemographic characteristics?

Are there letters of support from multiple potential partners, including holders of vital records, from which cases and controls will be identified, describing commitment of the partner organization to the project and any specified limits or terms of access to client information or data?

If the applicant proposes to include Spanish-speaking participants, do they have resources and staff expertise necessary to conduct the research in Spanish?

Has the applicant provided evidence for access to clinical space (potentially at multiple locations) to reasonably accommodate participants residing throughout the catchment area, or provided feasible non-clinic alternatives (e.g., home visits). Does the proposed clinic space and/or non-clinic alternatives offer sufficient availability to support the expected SEED Phase 3 participant volume with timely and flexible scheduling of the developmental assessment and phlebotomy participant visits?

Component B: Biorepository

Has the applicant provided evidence for high quality biosample repository facilities and staff expertise?

Component C: SEED 1 Follow-up Study

Has the applicant provided evidence for full access to both the data necessary to successfully implement a follow-up study of SEED 1 participants and the partnerships needed with relevant SEED 1 sites? Have agreements been reached for data access that comply with existing SEED data access infrastructure and with flexibility built in for any changes to that infrastructure?

2. Additional Review Criteria

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

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

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

(<http://www.cdc.gov/grants/additionalrequirements/index.html>).

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

Inclusion of Women, Minorities, and Children When the proposed project involves clinical research, the committee will evaluate the proposed plans for inclusion of minorities and members of both genders, as well as the inclusion of children. For additional information on review of the Inclusion section, please refer to the policy on the Inclusion of Women and Racial and Ethnic Minorities in Research (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.

Dual Use Research of Concern Reviewers will identify whether the project involves one of the agents or toxins described in the US Government Policy for the Institutional Oversight of Life Sciences Dual Use Research of Concern, and, if so, whether the applicant has identified an IRE to assess the project for DURC potential and develop mitigation strategies if needed. For more information about this Policy and other policies regarding dual use research of concern, visit the U.S. Government Science, Safety, Security (S3) website at: <http://www.phe.gov/s3/dualuse>. Tools and guidance for assessing DURC potential may be found at: <http://www.phe.gov/s3/dual-use/Pages/companion-guide.aspx>.

3. Additional Review Considerations

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

Applicants should submit a plan for data management and data sharing as a part of their application.

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. Investigators responding to this funding opportunity should include a plan on sharing research resources and data. This should include:

Use and support of the centralized web-based CADDRE Information System for data entry.

- Contribution of site-specific data to the SEED pooled dataset, which will be maintained and or overseen by CDC through their approved mechanism (maintained by the CADDRE DCC)
- Use of the CDC-approved mechanism for access and use of SEED analytic files, which will ensure that all CDC-required data security standards are maintained. (The currently approved mode for data access is via a remote data access server [RDA] maintained by the CADDRE DCC.)
- Willingness to implement procedures for contribution of site SEED Phase 3 genetic data to National Database for Autism Research (NDAR) and the Database for Genotypes and Phenotypes (dbGaP) at the end of the project.
- Adherence to CADDRE Data Sharing and Publication Guidelines for analysis, presentation, publication, and data release. The Guidelines promote and prioritize analyses using the SEED pooled data set (data from all 5 sites) above analyses based on single site data. Additionally the guidelines include CDC specific scientific requirements pertaining to CDC clearance of manuscripts and abstracts.

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/grants/additionalrequirements/index.html>. 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/grants/interestedinapplying/applicationresources.html>

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.

For Component A and C:

- Geographic diversity of recruitment sites.
- Diversity of study population by race/ethnicity

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 75, as appropriate, as well as any additional requirements included in the FOA.

Specific requirements that apply to this FOA are the following:

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

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

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

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

[AR-30: Information Letter 10-006, - Compliance with Section 508 of the Rehabilitation Act of 1973](#)

[AR 31 - Distinguishing Public Health Research and Public Health Nonresearch](#)

ARs applicable to Conference Awards:

[AR-20: Conference Support](#)

[AR-27: Conference Disclaimer and Use of Logos](#)

Organization Specific ARs:

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

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

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

3. Additional Policy Requirements

The following are additional policy requirements relevant to this 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/grants/contracts/contract-policies-regulations/efficient-spending/index.html>.

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

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

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/obesity/strategies/food-serv-guide.html>

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.

Pilot Program for Enhancement of Employee Whistleblower Protections All applicants will be subject to a term and condition that applies the terms of 48 CFR section 3.908 to the award and requires that grantees inform their employees in writing (in the predominant native language of the workforce) of employee whistleblower rights and protections under 41 U.S.C. 4712.

Copyright Interests Provision This provision is intended to ensure that the public has access to the results and accomplishments of public health activities funded by CDC. Pursuant to applicable grant regulations and CDC's Public Access Policy, Recipient agrees to submit into the National Institutes of Health (NIH) Manuscript Submission (NIHMS) system an electronic version of the final, peer-reviewed manuscript of any such work developed under this award upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. Also at the time of submission, Recipient and/or the Recipient's submitting author must specify the date the final manuscript will be publicly accessible through PubMed Central (PMC). Recipient and/or Recipient's submitting author must also post the manuscript through PMC within twelve (12) months of the publisher's official date of final publication; however the author is strongly encouraged to make the subject manuscript available as soon as possible. The recipient must obtain prior approval from the CDC for any exception to this provision. The author's final, peer-reviewed manuscript is defined as the final version accepted for journal publication, and includes all modifications from the publishing peer review process, and all graphics and supplemental material associated with the article. Recipient and its submitting authors working under this award are responsible for ensuring that any publishing or copyright agreements concerning submitted articles reserve adequate right to fully comply with this provision and the license reserved by CDC. The manuscript will be hosted in both PMC and the CDC Stacks institutional repository system. In progress reports for this award, recipient must identify publications subject to the CDC Public Access Policy by using the applicable NIHMS identification number for up to three (3) months after the publication date and the PubMed Central identification number (PMCID) thereafter.

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

Dual Use Research of Concern On September 24, 2014, the US Government Policy for the Institutional Oversight of Life Sciences Dual Use Research of Concern was released. Grantees (foreign and domestic) receiving CDC funding on or after September 24, 2015 are subject to this policy. Research funded by CDC involving the agents or toxins named in the policy, must be reviewed to determine if it involves one or more of the listed experimental effects and if so, whether it meets the definition of DURC. This review must be completed by an Institutional Review Entity (IRE) identified by the funded institution. Recipients also must establish an Institutional Contact for Dual Use Research (ICDUR). The award recipient must maintain records of institutional DURC reviews and completed risk mitigation plans for the term of the research grant, cooperative agreement or contract plus three years after its completion, but no less than eight years, unless a shorter period is required by law or regulation.

If a project is determined to be DURC, a risk/benefit analysis must be completed. CDC will work collaboratively with the award recipient to develop a risk mitigation plan that the CDC must approve. The USG policy can be found at

<http://www.phe.gov/s3/dualuse>.

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

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 part 75 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 Recipient will have the primary responsibility for the following:

Component A: CADDRE SEED Phase 3

- The Principal Investigator (PI) at each site will have the primary responsibility for oversight of project management and all scientific aspects of the project at their site and for the study overall in collaboration with other site Principal Investigators and the CADDRE Network Science Lead at CDC.
- The PI, project coordinator (PC), and other investigators at each site work collaboratively as members of the CADDRE Network and with the CDC CADDRE Network Science Lead and other CDC scientists and administrators on aspects of study implementation, data collection, and study conduct.
- While all CADDRE PIs worked collaboratively to develop the original SEED protocol for SEED 1 and consulted on revisions to the protocol in SEED 2, the protocol for SEED 3 (a streamlined version of the SEED 2 protocol) has already been developed by CDC and will not be changed significantly; this protocol was developed with the goals of maximizing data harmonization and containing costs for both the CADDRE Network and the supporting Data Coordinating Center.
- The PIs at each site and other members of the CADDRE Network will actively participate in CADDRE-wide meetings and webinars and CADDRE workgroup meetings and conference calls. The site PIs and PCs should plan to periodically attend in person CADDRE meetings in Atlanta, GA.

SEED 3 working groups and their responsibilities will likely include:

- PI Working Group: provides general oversight of all aspects of SEED with a particular focus on establishing SEED scientific priorities that guide study design, implementation, analysis, and publication.
- Data Sharing Committee: reviews and comments on all letters of intent for analyses, and manuscripts for publication.
- Biomarker Committee – a subgroup within the Data Sharing Committee that specifically reviews letters of intent for analyses proposing to use SEED bio-samples.
- Study Methods Working Group: advises on the methods for study, recruitment and follow-up of enrolled participants and to address any ad hoc concerns brought forward by other work groups about methodologic difficulties in collecting data from study participants.
- Clinician Working Group: oversees the use and quality control of psychometric assessments included in SEED. This includes considering whether, when, and how newer (updated) versions of standardized instruments used in SEED should be incorporated. This working group also reviews all of the human subjects issues related to these instruments e.g., developmental feedback letters, consent forms, etc.).
- Data Collection Working Group: This group previously developed nearly all SEED study-specific data collection instruments (i.e., instruments other than standardized psychometric forms). The group's role in SEED 3 will be to oversee quality control procedures for all of these instruments, particularly the maternal interview and the medical record abstractions.
- Project Coordinator Working Group: considers the study implementation plan and how to most practically implement the plan in consideration of the burden on the participants.
- Outreach Coordinators Working Group: promotes visibility of SEED by the public, community partners and potential participants to enhance general study awareness and recruitment efforts.
- All CADDRE sites must:
 - Obtain appropriate Institutional Review Board approvals for research involving human subjects for all participating sites and must adhere to CDC provisions of the Certificate of Confidentiality.
 - Ensure timely responses to all Quality Assurance/Quality Control (QA/QC) activities related to SEED.
 - Adhere to established CADDRE Publication and Data Sharing Guidelines. These guidelines include CDC specific scientific requirements pertaining to CDC clearance of manuscripts and abstracts.
 - Adhere to established procedures in support of the central web-based CADDRE Information System and Data Coordinating Center.
 - Provide site-specific SEED 3 data to the SEED pooled data set.
 - Use the CDC-approved mechanism for access and use of SEED analytic files, which will ensure that all CDC-required data security standards are maintained.

Component B: Biorepository

- The Principal Investigator (PI) for the Central Laboratory and Biorepository will have the primary responsibility for

oversight of all aspects of the project dealing with biosample collection, shipping, processing, DNA extraction, quality control, and storage in collaboration with CADDRE Network site Principal Investigators and the CADDRE Network Science Lead at CDC.

- The PI will be responsible for tracking biosamples and providing ongoing reports to the CDC and CADDRE Network.
- The Central Laboratory and Biorepository must:
 - Obtain appropriate Institutional Review Board approvals for research involving human subjects for all participating sites and must adhere to CDC provisions of the Certificate of Confidentiality.
 - Ensure timely responses to all Quality Assurance/Quality Control (QA/QC) activities related to SEED bio specimen collection.
 - Adhere to established CADDRE Publication and Data Sharing Guidelines
 - Adhere to established procedures in support of the central web-based CADDRE Information System and Data Coordinating Center.

Component C: SEED 1 Follow-up Study

- The Principal Investigator (PI) at each site will have the primary responsibility for oversight of project management and all scientific aspects of the project at their site and for the follow-up study overall in collaboration with other site Principal Investigators and the CADDRE Network Science Lead at CDC.
- The PI and project coordinator (PC) at each site work collaboratively as members of a SEED Follow-up Study Network and with the CDC CADDRE Network Science Lead and other CDC scientists and administrators on protocol development, study implementation, data collection, study conduct, and preparation of a feasibility report.
- The PIs and PCs in the SEED Follow-up Study Network will actively participate in Network meetings, webinars, and workgroups that might be established to address specific components of the study. The site PIs and PCs should plan to periodically attend in person meetings in Atlanta, GA.
- All SEED 1 Follow-up Study sites must:
 - Obtain appropriate Institutional Review Board approvals for research involving human subjects for all participating sites and must adhere to CDC provisions of the Certificate of Confidentiality.
 - Ensure timely responses to all Quality Assurance/Quality Control (QA/QC) activities related to SEED.
 - Adhere to Publication and Data Sharing Guidelines (to be established to be consistent with existing CADDRE Publication and Data Sharing Guidelines). These guidelines will include CDC specific scientific requirements pertaining to CDC clearance of manuscripts and abstracts.
 - Adhere to established procedures in support of the central web-based CADDRE Information System and Data Coordinating Center.
 - Provide site-specific data to the SEED 1 Follow-up Study pooled data set.
 - Use the CDC-approved mechanism for access and use of SEED analytic files, which will ensure that all CDC-required data security standards are maintained.

Component A and Component C

Recipient Organization's rights with respect to the information, data and software developed under this award are subject to applicable law and the U.S. Government rights of access consistent with current grants regulations and HHS/CDC policies.

Components A, B, and C

CDC staff have substantial programmatic involvement that is above and beyond the normal stewardship role in awards.

There are two separate CDC scientific roles – Scientific Collaborator (SC) and Scientific Program Official (SPO).

In this cooperative agreement, a NCBDDD SC (also known as the CADDRE Network Science Lead) and other NCBDDD scientific and administrative staff in the CADDRE Network and SEED Follow-up Network are partners with scientific and programmatic involvement during the conduct of the project through technical assistance, advice, and coordination. The SC will:

- 1) Support the grantees activities in development of the SEED 1 Follow-up Study protocol and support all activities for SEED 3 and the SEED 1 Follow-up Study: project implementation and management, data management and analysis, and adherence to CADDRE and SEED Follow-up Network and CDC guidelines for presenting research findings and publishing research reports;
- 2) Provide scientific consultation and technical assistance on epidemiologic and statistical methods, such as power calculations and response bias analyses;

- 3) Support the grantee of the Central Laboratory and Biorepository
- 4) Obtain Institutional Review Board approvals for the projects as required by CDC and other approvals that might be required, such as OMB PRA approval;
- 5) Chair the CADDRE Network PI WG and the Data Sharing Committee, participate in other CADDRE Network meetings and work groups and lead and participate in SEED Follow-up Study Network meetings and workgroups.
- 6) Participate in the QA/QC activities for all studies; and
- 7) Assist in the analyses, interpretation, and reporting of findings in the literature.

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

Additionally, an HHS/CDC agency program official will be responsible for the normal scientific and programmatic stewardship of the award. The SPO will be:

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

Areas of Joint Responsibility include:

Component A: CADDRE SEED Phase 3

The planning and implementation of the cooperative aspects of the study will be undertaken by the CADDRE site PIs and the CADDRE Network Science Lead at CDC. This group will work together in various work groups and committees including the PI Workgroup and the Data Sharing Committee.

These workgroups and committees will formulate plans for cooperative research and address issues of common concern throughout the life of the project. At periodic CADDRE meetings among all recipients, the groups will:

- 1) Discuss any difficulties in implementing the methodology for the study;
- 2) Identify how to reconcile differences in approaches to the study;
- 3) Identify and recommend solutions to unexpected study problems; and
- 4) Discuss ways to efficiently coordinate study activities and best practices.
- 5) The CADDRE data sharing committee will review and comment on requests to use the pooled SEED dataset for research analyses and publications resulting from these analyses.

Component B: Biorepository

The planning and implementation of the cooperative aspects of the study will be undertaken by the Central Laboratory and Biorepository PI and the CADDRE Network Science Lead at CDC with ongoing consultation from the CADDRE site PIs.

These groups will work together to

- 1) Identify and recommend solutions to unexpected study problems; and
- 2) Discuss ways to efficiently coordinate study activities and best practices.

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Component C: SEED 1 Follow-up Study

The planning and implementation of the cooperative aspects of the study will be undertaken by the SEED 1 Follow-up Study site PIs and the CADDRE Network Science Lead at CDC. This group will work to formulate plans for cooperative research and address issues of common concern throughout the life of the project. At periodic meetings among all recipients, the groups will:

- 1) Develop the final protocol for the follow-up study and feasibility assessment;

- 2) Discuss any difficulties in implementing the methodology for the study;
- 3) Identify how to reconcile differences in approaches to the study;
- 4) Identify and recommend solutions to unexpected study problems; and
- 5) Discuss ways to efficiently coordinate study activities and best practices.

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.

In addition to the reporting requirements outlined below in **B. Content of Reports**, grantees should include with their Yearly Non-competing Grant Progress Report:

- Human Subjects Education Requirement: Provide certification, for any new key personnel or other significant contributors involved in the design or conduct of research involving human subjects, that they have completed an educational program in the protection of human subjects.
- Report detailing current progress toward meeting all study target for enrollment and completion for Component A and Component C.

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, www.grants.gov 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: https://era.nih.gov/registration_accounts.cfm

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

Organizations may verify their current registration status by running the “List of Commons Registered Organizations” query found at: https://era.nih.gov/registration_accounts.cfm. Organizations not yet registered can go to <https://commons.era.nih.gov/commons/registration/registrationInstructions.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)
Telephone 770-488-2700 Email: PGOTIM@cdc.gov
Hours: Monday - Friday, 7am – 4:30pm U.S. Eastern Time

Scientific/Research Contact(s)

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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.

Sections 301(a) [42 U.S.C. Section 241(a)] and 317(C) of the Public Health Service Act [42 U.S.C. Sections 243, 247b (k) (2) and 247b-4], as amended.

Appendix A: SEED 1, 2, 3, 4 Comparison Tables

Table 1: Study Overview

Comparison SEED Phases -- Study Overview			
	SEED 1	SEED 2	SEED 3
Sites			
Funding period (s)	2001-2006, 2006-2011	2011-2016	2016-2021
Number sites funded	5	5	4
CDC participate as additional site?	yes	yes	yes
Total number sites	6	6	5
Overview study design and implementation			
Study design	case-control	case-control	case-control
Target population birth cohorts	2003-2006	2008-2011	2014-2017
Size of target populations	~33,000-52,000 births/site	~33,000-52,000 births/site	TBD
Field work enrollment time period	2007-2011	2012-2015	2017-2021
Field work data collection time period	2007-2012	2012-2016	2017-2021
Study groups enrolled	Cases: children with autism spectrum disorder(ASD) + 2 control gps: other developmental disabilities (DD) and population controls (POP)	Cases: children with autism spectrum disorder(ASD) + 2 control gps: other developmental disabilities (DD) and population controls (POP)	Cases: children with autism spectrum disorder(ASD) + 2 control gps: other developmental disabilities (DD) and population controls (POP)
Recruitment and enrollment details			
ASD ascertainment sources	multiple clinical and school sources in target population	multiple clinical and school sources in target population	multiple clinical and school sources in target population
DD ascertainment sources	multiple clinical and school sources in target population	multiple clinical and school sources in target population	multiple clinical and school sources in target population
POP ascertainment source	sample of birth records in target population	sample of birth records in target population	sample of birth records in target population
Recruitment methods (standard)	Intital contact was via mailing. Non-responders sent repeat mailings and/or were contacted via telephone call or email (maximum of 9 contact attempts) after 2 weeks non-reponse to initial mailing. Specific nonresponse protocol varied by site.	Intital contact was via mailing. Non-responders sent repeat mailings and/or were contacted via telephone call or email (maximum of 9 contact attempts) after 2 weeks non-reponse to initial mailing. Specific nonresponse protocol varied by site.	Same as SEED 1 and SEED 2 but all sites encouraged to seek permissions to actively contact non-responders via telephone calls and email to extent possible.
Recruitment enhancements from previous SEED phase	NA	Incentives added for all invited families to encourage contact and participation in eligibility screen even if study participation refused; increased outreach in communities; enhanced tracing (some sites); streamlined protocol less burdensome.	Sites encouraged to seek permissions to actively contact non-responders via telephone calls and email to extent possible; protocol further streamlined to be less burdensome.
Use of Self referrals to increase ASD numbers	minimal	YES (variable by site)	NO -- practice discontinued

Eligibility Criteria			
Child Born in study birth yr range	YES	YES	YES
Child resident of site catchment area at birth	YES	YES	YES
Child current resident catchment area	YES	YES	YES
Child living with knowledgeable caregiver or biologic mother from 6 months of age	YES -- residence with knowledgable caregiver sufficient	YES -- residence with biological mother required	YES -- residence with biological mother required
Caregiver/mother able to provide legal consent	YES	YES	YES
Caregiver/biologic mother able to communicate in English OR English and Spanish (variable by site)	YES	YES	YES
Child physically able to complete developmental assessment	YES	YES	YES
Child aged 30-68 months at time of developmental assessment	YES	YES	YES
Case classification and study workflow groups			
Social Communication Questionnaire used as autism screen	YES	YES	YES
Final ASD classification based on ADOS and ADI-r results	YES	YES	YES
Case Ascertainment Mechanism Used: Invite and enroll children with previous ASD dx or autism special ed classification + Invite children with other developmental dx and special ed classification. Screen ALL enrolled children in all 3 study groups for possible autism with SCQ. All children with previous ASD dx/sp ed classification come in as presumptive cases. All children in all groups (including DD and POP) who screen "+", SCQ => 11 (low threshold to increase sensitivity), also come in as presumptive cases. All presumptive cases slated for in depth developmental assessment including ADOS and ADI-r. Final case classification based on results of ADOS and ADI-r. Some children who are presumptive cases do not meet criteria for final case. Their final classification will usually be DD with a designation that they had some ASD symptoms. (some children in presumptive case group go back to POP as final classification). A priori algorithm used to determine how children are assigned into various study workflows ASD or DD/POP and how final classification is assigned.	YES	YES	YES
Study flow ASD includes in person assessment	YES	YES	YES
Study flow POP (with SCQ <11) includes in person assessment -- but with less testing	YES	YES	YES
Study flow DD (with SCQ <11) includes in person assessment -- but with less testing	YES	YES	NO -- protocol shortened for this group

Incentives/Compensation			
Incentives -- do all invited participants receive \$10 incentive if they take eligibility screen whether or not they enroll?	NO	YES	YES
Incentives/Compensation if all study steps completed: ASD (case) workflow	\$315	\$325	\$325
Incentives/Compensation if all study steps completed: POP (SCQ<11) workflow	\$235	\$200	\$200
Incentives/Compensation if all study steps completed: DD (SCQ<11) workflow	\$235	\$200	\$125
Study protocol overview			
Study protocol - data collection -- full description in separate tables	multiple modes of data collection including maternal interview on sociodemographics and reproductive and pregnancy health, multiple self-administered forms on parents' and child's health and development; medical record abstractions (mother and child), in person child developmental assessment, in person dysmorphology assessment, and collection of biospecimens from both parents and child	Still comprehensive but streamlined: multiple modes of data collection including maternal interview on sociodemographics and reproductive and pregnancy health, multiple self-administered forms on parents' and child's health and development; medical record abstractions (mother and child), in person child developmental assessment, and collection of biospecimens from mother and child and limited biospecimens from father	Still comprehensive but streamlined even further: multiple modes of data collection including maternal interview on sociodemographics and reproductive and pregnancy health, multiple self-administered forms on parents' and child's health and development; medical record abstractions (mother) in person child developmental assessment, and collection of biospecimens from mother and child and limited biospecimens from father
Study protocol -- data collection -- same for each group	DD and POP workflow same study protocol; ASD workflow -- more in depth developmental assessment and a few extra forms	DD and POP workflow same study protocol; ASD workflow -- more in depth developmental assessment and a few extra forms	DD and POP workflow no longer the same; DD workflow is greatly streamlined such that in person visit, medical record abstraction and biospecimens no longer included. POP workflow streamlined but similar generally to SEED 2 protocol. ASD workflow streamlined but similar generally to SEED 2 protocol including more in depth developmental assessment and a few extra forms
Birth record requirement			
Requirement to link SEED data to birth records	YES -- enrolled subjects only	YES -- enrolled subjects only	YES -- enrolled subjects required; sites also asked to seek limited birth record data on all invited participants to assess non-response.
Ancillary support			
CDC funds biorepository to support SEED	YES	YES	YES

CDC funds data coordinating center to support SEED	YES	YES	YES

Table 2: Study Targets

Comparison SEED Phases --Target enrollment and completion numbers and rates			
	SEED 1	SEED 2	SEED 3
Target enrollment ratio ASD:DD:POP	1 to 1 to 1	1 to 1 to 1	1 to 1 to 1
Target study enrollment and completion numbers / study group (all sites combined)	650 enrolled subjects with complete data on study protocol steps	750 enrolled subjects with complete data on study protocol steps	625 enrolled subjects with complete data on study protocol steps
Target study completion numbers /study group / site	108 enrolled subjects with complete data on study protocol steps	125 enrolled subjects with complete data on study protocol steps	125 enrolled subjects with complete data on study protocol steps
Did all sites meet enrollment - completion targets in all groups?	NO, but some sites exceeded so total number was met	TBD	TBD
Final number enrolled/complete ASD (all sites combined) (enrolled estimated as final class CASE + possible case)	1276 / 707	TBD	TBD
Final number enrolled/complete DD	1270 / 995	TBD	TBD
Final number enrolled/complete POP	1223 / 898	TBD	TBD
Additional children enrolled -- siblings of index children (not counted in above numbers)	YES -- low number siblings (especially twins) born in same birth year range enrolled for special studies: requirement was that at least one had to be presumptive ASD	NO	NO
Additional response rate and completion rate targets included in FOA	NO	NO	YES: Response rate targets: 50% source class ASD; 40% source class DD; 30% POP Completion rate targets: 75% in all groups

Table 3: Data Collection Overview

Comparison SEED Phases -- Data collection protocol - Overview of what was included and what changed between SEED phases Included=included in SEED 1 Not included=not included in SEED 1; Same=included and same as previous phase; Minor revision=minor revisions only (streamlining and limited revisions or added questions); Moderate revision=moderate revision but generally because items from other forms moved to the current form/exam; Major revision=major revision; New but mostly old items=New form/exam that incorporates streamlined versions of several discontinued forms/exams; New=new form/exam; Discontinued certain WF=form/exam no longer included in certain workflows in which it was previously included; Discontinued=form/exam completely discontinued in this phase of SEED (although some items might have been moved to other forms in a streamlined fashion)			

	SEED 1	SEED 2 in comparison to SEED 1	SEED 3 in comparison to SEED 2
Eligibility screen at start of enrollment	Included	Minor Revision	Same
SCQ upon enrollment -- phone interview	Included	Same	Same
Pregnancy reference form (to prepare for longer maternal interview) -- 15 min phone interview	Included	Minor Revision	Same
Caregiver or Maternal interview -- 60 minute phone interview (most is on mother's reproductive health hx and pregnancy with index child)	Included	Minor Revision	Same
Maternal medical hx form -- self administered	Included	Moderate Revision	Same
Paternal medical hx form -- self administered	Included	Moderate Revision	Same
Paternal occupational hx form -- self administered	Included	Discontinued	
Family autoimmune disorders hx form -- self administered	Included	Discontinued	
Child GI health form -- parent administered	Included	Discontinued	
Child sleep hx form -- parent administered	Included	Discontinued	
Child health hx Form -- parent administered	Not included	New but mostly old items	Same
Child services and treatment Q -- parent administered	Included	Major revision	Same
Maternal and child residency hx form -- self administered	Not included	New	Same
Child behavior checklist (CBCL) -- standardized form self administered	Included	Same	Discontinued certain WF
Social responsiveness scale (child) -- parent administered	Included	Same	Discontinued certain WF
Social Responsiveness Scale (both parents) --parent administered for each other	Included	Discontinued	
Carey temperament scale -- parent administered	Included	Discontinued	
Early development questionnaire -- parent administered	Included	Discontinued	
Mullen scales of early learning -- in person assessment	Included	Same	Discontinued certain WF
Vineland adaptive behavior scales -- in person interview mother	Included	Same	Discontinued certain WF
Autism diagnostic observation scale (ADOS) -- in person assessment	Included	Same	Same
Autism diagnostic interview revised (ADI-r) -- in person interview mother	Included	Same	Same
Full dysmorphology assessment (including anthropometry)	Included	Discontinued	
Child anthropometry only	Not included	New but mostly old items	Discontinued certain WF
Child buccal or saliva	Included	Minor Revision	Discontinued certain WF
Mother buccal or saliva	Included	Minor Revision	Discontinued certain WF
Father buccal or saliva	Included	Minor Revision	Discontinued certain WF
Child blood	Included	Same	Discontinued certain WF
Mother blood	Included	Same	Discontinued certain WF

Father blood	Included	Discontinued	
Child hair sample	Included	Discontinued	
Maternal prenatal care medical record abstraction	Included	Minor Revision	Discontinued certain WF
Maternal labor and delivery medical record abstraction	Included	Minor Revision	Discontinued certain WF
Child pediatric care medical record abstraction	Included -- Major revision during the study phase	Same	Discontinued
Child neonatal care medical record abstraction	Included	Minor Revision	Discontinued
Child 3 day diet diary	Included	Discontinued	
Child 7 day stool diary	Included	Discontinued	

Table 4: Data Collection by WorkFlow

Comparison SEED Phases -- Data collection protocol according to WF			
ASD = all ASD workflow, regardless of original source class or final case classification; DD = DD source class with SCQ<11; POP = POP source class with SCQ<11			
	SEED 1	SEED 2	SEED 3
Eligibility screen at start of enrollment	ASD, DD, POP	ASD, DD, POP	ASD, DD, POP
SCQ upon enrollment -- phone interview	ASD, DD, POP	ASD, DD, POP	ASD, DD, POP
Pregnancy reference form (to prepare for longer maternal interview) -- 15 min phone interview	ASD, DD, POP	ASD, DD, POP	ASD, DD, POP
Caregiver or Maternal interview -- 60 minute phone interview (most is on mother's reproductive health hx and pregnancy with index child)	ASD, DD, POP	ASD, DD, POP	ASD, DD, POP
Maternal medical hx form -- self administered	ASD, DD, POP	ASD, DD, POP	ASD, DD, POP
Paternal medical hx form -- self administered	ASD, DD, POP	ASD, DD, POP	ASD, DD, POP
Paternal occupational hx form -- self administered	ASD, DD, POP		
Family autoimmune disorders hx form -- self administered	ASD, DD, POP		
Child GI health form -- parent administered	ASD, DD, POP		
Child sleep hx form -- parent administered	ASD, DD, POP		
Child health hx Form -- parent administered		ASD, DD, POP	ASD, DD, POP
Child services and treatment Q -- parent administered	ASD	ASD	ASD
Maternal and child residency hx form -- self administered		ASD, DD, POP	ASD, DD, POP
Child behavior checklist (CBCL) -- standardized form self administered	ASD, DD, POP	ASD, DD, POP	ASD, POP
Social responsiveness scale (child) -- parent administered	ASD, DD, POP	ASD, DD, POP	ASD, POP
Social Responsiveness Scale (both parents) --parent administered for each other	ASD, DD, POP		

Carey temperament scale -- parent administered	ASD, DD, POP		
Early development questionnaire -- parent administered	ASD		
Mullen scales of early learning -- in person assessment	ASD, DD, POP	ASD, DD, POP	ASD, POP
Vineland adaptive behavior scales -- in person interview mother	ASD (all) DD and POP (with indication only)	ASD (all) DD and POP (with indication only)	ASD (all), POP (with indication only)
Autism diagnostic observation scale (ADOS) -- in person assessment	ASD	ASD	ASD
Autism diagnostic interview revised (ADI-r) -- in person interview mother	ASD	ASD	ASD
Full dysmorphology assessment (including anthropometry)	ASD, DD, POP		
Child anthropometry only		ASD, DD, POP	ASD, POP
Child buccal or saliva	ASD, DD, POP	ASD, DD, POP	ASD, POP
Mother buccal or saliva	ASD, DD, POP	ASD, DD, POP	ASD, POP
Father buccal or saliva	ASD, DD, POP		
Child blood	ASD, DD, POP	ASD, DD, POP	ASD, POP
Mother blood	ASD, DD, POP	ASD, DD, POP	ASD, POP
Father blood	ASD, DD, POP		
Child hair sample	ASD, DD, POP		
Maternal prenatal care medical record abstraction	ASD, DD, POP	ASD, DD, POP	ASD, POP
Maternal labor and delivery medical record abstraction	ASD, DD, POP	ASD, DD, POP	ASD, POP
Child pediatric care medical record abstraction	ASD, DD, POP	ASD, DD, POP	
Child neonatal care medical record abstraction	ASD, DD, POP	ASD, DD, POP	
Child 3 day diet diary	ASD, DD, POP		
Child 7 day stool diary	ASD, DD, POP		