
NIH Request for Information:
Inviting Comments and Suggestions on the
Environmental influences on Child Health
Outcomes (ECHO) Program (the National
Children's Study Alternative)

Analysis of Public Comments

November 2015

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Executive Summary

In 2000, Congress authorized the National Children's Study (NCS) as part of the Children's Health Act. Subsequent expert reviews expressed concerns about the study's progress, and after careful consideration and discussion, NIH Director Francis Collins accepted the Advisory Committee to the NIH Director's (ACD) recommendation to discontinue the NCS in December 2014. Using FY15 funds, NIH leadership and staff identified opportunities to develop tools to enhance measurement of environmental exposures and facilitate research across initiatives and programs. Going forward for FY16 and beyond, NIH leadership and staff developed a proposal, named the Environmental influences on Child Health Outcomes (ECHO) program, to support multiple synergistic, longitudinal studies using extant cohorts that capture variable environmental exposures, share standardized research questions, and focus on key pediatric outcomes. As part of the effort to disseminate the draft proposal and to solicit input from the public, NIH released a Request for Information (RFI): Inviting Comments and Suggestions on the Environmental influences on Child Health Outcomes (ECHO) Program (the National Children's Study Alternative) ([NOT-OD-15-117](#)).

The RFI requested input from researchers and other stakeholders in the research community, and asked for comments on the proposal to harmonize extant cohorts, on the core elements and focus areas, and on an additional proposal to fund a National IDeA States Pediatric Clinical Research Network. A web-based form for submitting comments was available from July 14, 2015 to August 14, 2015. During this period, NIH received 184 responsive submissions from individuals and organizations representing academic institutions, advocacy and professional groups, hospitals, and other constituencies.

Responses to the RFI largely supported the goals of the original NCS and of the ECHO proposal to leverage extant cohorts to accomplish similar goals. Many respondents commented on the challenges inherent to the synthesis and harmonization of existing studies, and provided constructive suggestions and considerations for management. Respondents also provided additional topics that they suggested be incorporated into the ECHO program, including specific environmental exposures and child health outcomes. One repeated concern was the perceived emphasis on biological factors and the perceived lack of emphasis on the social environment, broadly construed; respondents frequently cited the importance of understanding the social determinants of child health. Many respondents also provided specific and detailed information on existing cohorts that could provide valuable or unique contributions to the overarching ECHO endeavor. Finally, respondents generally supported the proposal for an IDeA States Pediatric Clinical Research Network, citing the potential to reach otherwise underserved populations.

Report on the Results of the RFI

Introduction

In 2000, Congress authorized a study of children's health and development, the National Children's Study (NCS), as part of the Children's Health Act. After a period of development, reviews by the Institute of Medicine (IOM) and a working group of the Advisory Committee to the Director (ACD) of NIH expressed concerns about the study's design, management, oversight structure, and anticipated cost. After careful consideration and discussion with NIH senior leadership, NIH Director Francis Collins accepted the ACD's recommendation to discontinue the NCS in December 2014.

Subsequently, NIH leadership and staff worked diligently to identify opportunities to address challenges at the intersection of pediatric and environmental health through alternative approaches that are consistent with the original goals of the NCS. These opportunities included establishing compelling new programs, integrating existing programs, and enhancing programs by incorporating more comprehensive environmental assessments. Going forward, NIH proposes to support multiple synergistic, longitudinal studies using extant cohorts that capture variable environmental exposures (e.g., physical, chemical, biological, psychosocial, natural and built environments) and that will share standardized research questions and focus on four key pediatric outcomes with high public health impact. This initiative is named the Environmental influences on Child Health Outcomes (ECHO) program. Initially, the draft framework of this program consisted of Core Elements and Focus Areas:

- The Core Elements to be addressed across all studies are:
 - Demographics
 - Typical early development
 - Epigenetic influences on early childhood development
 - Environmental factors
- Four focus areas will address critical pediatric conditions or health outcomes to assess range of functioning over time:
 - Upper and lower airway
 - Obesity
 - Pre-, peri-, and postnatal outcomes
 - Neurodevelopment
- As an additional research opportunity, the plan also proposes to create an IDeA States National Pediatric Clinical Research Network, which could:
 - Address access gaps for rural children through a national network for pediatric research embedded at IDeA locations
 - Link existing IDeA state centers with experts in clinical trials

NIH leadership solicited feedback from the public and other stakeholders on the ECHO proposal, in order to identify emerging scientific opportunities and gather suggestions for how to improve the draft framework. Part of the efforts to disseminate the proposed plan and solicit input included a Request for Information (RFI): Inviting Comments and Suggestions on the Environmental influences on Child Health Outcomes (ECHO) Program (the National Children's Study Alternative) ([NOT-OD-15-117](#)). Comments were accepted online from July 12, 2015 to August 14, 2015. NIH invited community feedback on several topic areas:

- The Core Elements:
 - Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements
 - Additional core elements to be considered
 - Considerations for harmonizing data across cohorts
 - High impact areas of opportunity in addition to those listed
 - Anticipated advances and/or considerations for implementing state of the art data collection and analytic methodologies throughout the duration of the study
- The four Focus Areas:
 - Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)
- The additional IDeA States opportunity

Characteristics of Respondents:

NIH received 187 submissions to the RFI, including three duplicate submissions. Of the responsive submissions, 114 (62 percent) were submitted by individuals and 70 (38 percent) were submitted on behalf of organizations or groups. Individuals who provided comments included 87 representatives from academic institutions, nine from private hospitals or companies, seven from the biotechnology industry, four from government, four private citizens, and three from patient advocacy organizations or research foundations. The organizations and groups providing responses included 22 professional societies or associations, 19 academic institutions, 11 private hospitals or companies, 10 patient advocacy organizations or research foundations, four from government, and four from the biotechnology industry. Some organizational responses were endorsed or signed by multiple people; in these cases, the group was counted as a single respondent.

Analysis of the Results:

RFI respondents were invited to give feedback on the topic areas outlined above. NIH staff analyzed the content of these responses using a standardized coding structure (See Table A1 in the Appendix for a description of the codes and sub-codes used in the analysis, along with sample responses). Codes were not mutually exclusive; response statements could be assigned to multiple codes as necessary. Some respondents provided narrative statements rather than responses to the individual RFI questions. The narrative content was coded according to the same structure as other responses.

Comments on Leveraging Existing Cohorts

A key component of the ECHO program is the plan to leverage existing cohorts into a combined synthetic cohort, and almost all responses discussed the various implications of this plan at different levels of detail. While many of the responses summarized below also related to the plan to leverage existing cohorts, many comments explicitly focused on the benefits, challenges, and implications of this plan. Respondents acknowledged that leveraging existing cohorts represents an efficient use of existing resources and an increased return on investment (42).

Respondents also discussed general management issues related to combining existing cohorts, including infrastructure, staffing, and communications; some comments referenced whether and how NIH should play a role in the management, including issues related to funding mechanisms (7). Other comments related to the integration of existing cohorts (26). These respondents expressed concern that incoming ECHO investigators be allowed flexibility to maintain the potentially disparate original aims of their extant cohorts, and that those original goals (which have already been deemed valuable to the funding Institutes and Centers) not be lost among the overarching aims of the ECHO program. These respondents also highlighted the value of potential collaboration among cohort investigators, and of potential interdisciplinary links generated by the program.

Given that extant cohorts focus on different populations and health topics, several respondents (13) suggested that NIH conduct a thorough survey of these cohorts. These respondents pointed to the value that such a survey would have in evaluating the strengths and weaknesses of incoming applications for the ECHO program, and for identifying gaps that this initiative could be uniquely positioned to address.

Suggestions and Comments Related to Data Harmonization

Almost all respondents commented in some way on considerations related to harmonization and synthesis of data from the various existing cohort data sets that could be incorporated into the ECHO program. These comments ranged from the broad implications of the history and content of existing data sets, to recommendations for specific harmonization strategies and techniques. A number of comments (44) expressed concerns that, although relatively similar data may have been collected across a variety of extant cohorts, variability in data collection practices, instrumentation, and storage could limit the extent to which harmonization is possible. However, other comments (19) highlighted specific benefits of combining data sets in some format, including increased sample sizes to power additional analyses, and the ability to pursue research questions that would otherwise be infeasible.

In addition to the general comments on project management described above, respondents also commented specifically on the management of data from a range of extant cohorts (23). These comments indicated that a strong system of data and study coordination would be essential to both harmonization of retrospective data as cohorts become integrated into the ECHO infrastructure, and in establishing common data elements for any prospective data yet to be collected. A related set of comments (16) focused on the establishment of metadata and ontology for establishing common data elements. These respondents cited the need for a fully annotated data dictionary to evaluate cross-study integration, and systems and applications for notation and communication of metadata. Several respondents also commented that extensive data harmonization efforts may cost more than would be warranted given the anticipated outcome (7).

Respondents also focused on issues related to the data set that will result from the harmonization of extant cohort data. Some commented on ethical principles related to experimenters' access to and use of data (5), and some indicated that data from the ECHO program be made relatively open to public or broad scientific access, rather than being restricted exclusively to participating investigators (13).

Given the range of strategies available for consideration in harmonizing data, a number of commenters provided "lessons learned" in the form of either previously successful harmonization efforts, or sources of relevant expertise (42). Several comments noted the specific parameters and caveats of previous efforts to harmonize existing data sets. Respondents also advocated for the involvement of certain types

of experts, including social scientists, demographers, and biostatisticians, as essential to the rigorous process of harmonizing existing data sets.

A final set of comments related to data considerations focused on the process of harmonization (19); respondents suggested that harmonization be considered a creative, open, and scientifically-grounded process rather than an administrative one.

Suggestions and Comments Related to ECHO Cohort Participants

The intended nation-wide breadth of the original National Children's Study recruitment prompted many respondents to comment on aspects of the participant composition for the ECHO program (91). Of these, approximately one-third (35) stressed the need to recruit a diverse sample of participants from various racial, ethnic, geographic, and socioeconomic backgrounds. These comments were distinct from those, discussed below, that highlighted social, family, neighborhood, and cultural factors as important environmental influences to capture. Other comments (17) highlighted the value of using probability sampling strategies to generate samples representative of the U.S. population, given the need to draw valid conclusions about exposure, prevalence, and risk for U.S. children. Of these, several comments specifically pointed to limitations of clinic-based and other convenience sampling methods.

Related responses (17) expressed concern about representativeness and recruitment strategies used by extant cohorts, and therefore advocated for the recruitment of new dedicated cohorts and/or samples for the ECHO program, rather than focusing exclusively on the stated plan to synthesize existing cohorts.

Several respondents (4) raised considerations related to re-consenting participants in existing cohorts for additional data collection or data use, or commented on consent to participate and use data from sovereign tribal populations.

Suggestions and Comments Related to Biological and Environmental Samples

Beyond the responses related to harmonization of existing data sets discussed above, several commenters (28) focused specifically on existing biological and environmental samples that may have been collected by the incoming ECHO cohorts. Of these responses, the majority (21) acknowledged that while extant cohorts may have collected samples related to some of the core elements listed in the RFI, and may have biospecimens available in some quantity for further analysis, some specimens may be missing entirely or in insufficient quantities to be effectively merged into the broader data set. These responses also included concerns that the methodological details of specimen collection and storage may vary across extant cohorts, leading to complications in harmonizing and collectively analyzing those samples. Several respondents highlighted the importance of collecting data during pregnancy, and further, doing so prospectively rather than retrospectively, due to concerns about recall bias.

Further, in addition to comments about the existence and quantity of biospecimens, several (7) focused more generally on the need or specifications for a biorepository, and other considerations for biological specimens.

Suggestions and Comments Related to Areas of Scientific Opportunity

Overall, comments clearly supported the Core Elements and Focus Areas identified in the RFI as crucial child health areas where sustained and thoughtful investment could result in significant progress. However, with few exceptions, respondents also took the opportunity to suggest additional topics of study for the ECHO program. Of these, many provided specific environmental exposures to be added to those listed in the RFI (95). Some of these focused on maternal pre-pregnancy measures and assessment of pregnancy conditions, in addition to child measures, arguing that understanding the role of these earliest exposures would be particularly beneficial. Other comments suggested specific child health outcomes to be added to those listed in the RFI (45). These respondents generally argued that adding a particular suggested exposure or outcome would meaningfully improve the impact and benefit of the ECHO program.

Finally, other respondents took a more general approach, suggesting additional broad scientific areas that they considered relevant to the goals of this initiative (51). These comments did not name specific additional exposures (e.g., chemical compounds), or diseases and conditions (e.g., asthma), but rather described broad areas of study, fields, or scientific orientations. Several comments focused on the perceived emphasis, as described in the RFI, on biological exposures and outcomes relative to social and cultural contexts and outcomes. These comments often highlighted the breadth and complexity of the social environment, encompassing parental and family relationships along with community and economic factors. Likewise, some commenters discussed the value of multigenerational data for understanding health outcomes. Other respondents highlighted expertise found in the population social sciences, and suggested either that these scientists be involved in the design and implementation of the ECHO program, or that existing social science cohorts be considered as candidates.

Suggestions and Comments Related to Existing Resources

Similarly, it was extremely common for respondents to identify specific existing resources relevant to the ECHO program. Almost half of all respondents (98) provided information about one or more extant cohorts that could potentially be incorporated into the initiative. Many of these comments provided extensive detail about the existing cohort studies, including information about sample composition and size, exposure and outcome measures, and study staff expertise and infrastructure. Respondents also pointed out potentially unique or high-impact contributions that particular existing cohorts could make to the overall effort.

A smaller, but still substantial, number of respondents (38) discussed additional sources of information that could be useful in designing data collection and/or participant ascertainment strategies for the ECHO program. Several respondents suggested integration of electronic health records (EHRs), citing their increasing availability within health systems and the fact that they capture health and outcome information specifically in line with the current aims.

Suggestions and Comments Related to the Proposed IDeA States National Pediatric Clinical Research Network

Overall, fewer respondents (44) commented on the proposed IDeA States National Pediatric Clinical Research Network, relative to the topics outlined above. However, those comments were generally enthusiastic about both the general idea of engaging additional research infrastructure in IDeA states,

and specifically the proposal described in the RFI. Respondents emphasized the ability of the proposed IDeA Network to reach out to rural and underserved populations that are not typically enrolled in biomedical research (17). However, some respondents (12) expressed concern that, while perhaps having merit on its own, this proposal did not fit the original intent of the National Children's Study or of the other components of the broader ECHO initiative.

Summary and Conclusions

The RFI responses included a range of suggestions for effective and impactful implementation of the proposed ECHO program. Respondents came largely from the academic and research community, and appeared to represent both those who had experience working with cohort studies like those referenced in the RFI, as well as those who could provide complementary or alternative perspectives. A number of advocacy groups and professional associations and societies also provided responses. Many respondents referred to lessons learned from the National Children's Study, and suggested strategies whereby the ECHO program could achieve the initial goals of the NCS.

In general, responses to the RFI emphasized the great potential value of the knowledge to be gained through the ECHO program, alongside the great potential challenges inherent in such a large and broad program. Commenters favored the general approach of synthesizing existing cohorts, given the expertise and breadth that they represent, but cautioned strongly that both extensive data harmonization and strong programmatic oversight would be essential to valid synthesis. Respondents provided detailed and specific recommendations for particular data harmonization and management strategies, and cited previous examples of combined cohort data sets.

Many respondents agreed that the Core Elements and Focus Areas proposed in the RFI reflect relevant and high-priority areas for child health research. The breadth of the ECHO program was largely seen as a strength, and indeed, respondents often commented that components could be added to additionally leverage the infrastructure and investment that ECHO will represent. Respondents also suggested many additional topics, either as distinct elements or focus areas, or as revisions or adjustments to the elements and focus areas described in the RFI.

One overarching theme that emerged was respondents' desire to see greater explicit emphasis or inclusion of social factors in addition to biological and physical factors. This theme was reflected in frequent comments highlighting the importance of the social environment, very broadly construed, as a determinant of child health. This theme was also reflected in the suggestion of social science, demography, and epidemiology, among other fields, as relevant sources of expertise. These research areas were cited as sources of potential collaborators in the development and implementation of ECHO, as well as providing evidence for best practices and strategies for conducting large-scale studies of public health.

Fewer respondents commented on the proposed IDeA States Pediatric Clinical Research Network relative to the rest of the ECHO proposal. However, these comments were largely positive and cited the benefit of outreach to underserved populations that this proposal could accomplish.

NIH appreciates the feedback received through this RFI and will consider the comments and suggestions when further developing and implementing the ECHO program.

Acknowledgements

The NIH-wide ECHO Working Group

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Appendix

Coding Table and Selected Comments

The comments in the table below are taken directly from the RFI responses.

Primary Category	Code	Selected Comment(s)
Leveraging existing cohorts	Return on investment	leveraging existing successful networks by expanding the scope to include RFI priorities would be cost efficient (29)
		maximizes resources already expended (97)
	Management	in planning the utilization of existing cohorts, it is imperative that cross-cohort oversight committees be formed to decide what and how samples will be collected and stored as the studies continue (43)
	Integration	the investigators that developed [existing] cohorts should be “at the table” and included in the design and implementation of any future studies (105)
		the collaboration of multiple groups and multiple ideas instead of competitive disputes will provide the necessary gain for better understanding (84)
	Survey	an inventory of existing cohorts can help point to the most pressing needs (71)
Other	it is essential that ECHO involve extramural research grants, not just extramural researchers (31)	
Data considerations	Limitations	definitions of data elements already collected are likely to vary between studies (184)
		harmonization will depend not just on the wording of the questionnaire items that are administered to respondents, but also to a great degree on survey mode, interviewer training interview protocols and procedures, efforts by interviewers to clarify questions to respondents and to minimize item nonresponse, respondent incentives, and the context in which interviews are obtained (143)
		if the samples chosen are too small, even with rich, dense longitudinal data, it would be extremely difficult to weave a number of these smaller studies together to form a cohesive, functional, and representative data base (139)
		data collected in different cohorts will most likely be maintained using customized hardware and software, management plans and data formats, all of which may hinder or delay data analysis (110)
	Benefits	pooled results can increase the generalizability of results, help uncover effects of interest that are small but important, and increase the number of observations of infrequent results (150)
		the key benefit is the larger sample which enable not only multiple exposure variables (e.g., chemical or nutritional mixtures/combinations, epigenomic and genomic regions) to be evaluated in relation to common outcomes including early signs of obesity, neurodevelopmental outcomes,

		cardiometabolic risk and even malignancies, while adjusting for covariates (153)
	Management	existing cohorts will already have a data coordinating center or data management structure in place. Continued involvement of the cohort’s data experts will be necessary for data harmonization in the initial phase of the ECHO program (170)
		having a well-established, scientifically sound and solid platform for data collection and management, and minimizing protocol changes in the midst of data collection will be crucial to successful data collection. That said, the platform should also not be set in stone, and be adaptive as new knowledge is acquired during the course of the research over several years (175)
	Ontology	metadata can be automatically compared to assess the similarity and differences between data items to make measurement recoding more efficient (63)
		one of your first tasks will be to create a data dictionary for each existing cohort to adequately document the date elements available, how/where/how often/on whom they were collected, codes that were used (11)
	Cost	a major consideration is the cost and burden on investigators to work through what information is comparable or can be harmonized and what cannot, and then how to do it (187)
	Ethics	the “usual” issues of privacy and confidentiality will be exacerbated by there being not only personally identifiable information, but also institutionally identifiable information (115)
		ECHO has the opportunity to broaden the communities of science who are concerned about child health and who could, working together, generate truly innovated data sets (168)
	Access	what data ownership and publication rights will individual investigators have over prior vs. new data collection, assuming a harmonized model with a central coordinating center (50)
	Examples or resources	in the MeDALL consortium, data has been combined and being analyzed for over 20,000 participants (127)
		social and population scientists have extensive experience working with multiple large and complex data sets and harmonizing the data for research (31)
		Consider, for example, the post-hoc harmonization of the National Health Interview Survey, called the “Integrated Health Interview Survey.” This project, conducted by the Minnesota Population Center (in collaboration with the National Center for Health Statistics), has resulted in substantial growth in the use of that national representative data set to US study health trends across time (174)
	Other	this would be an outstanding opportunity to use machine learning methods to determine which of several factors are most influential in developmental outcomes (12)
Cohort participant considerations	Probability sampling	having a nationally representative sample that can provide generalizable information about children provides the most benefit to address the needs of America’s children by reflecting their status and the areas in which policy and development of health programs should focus (119)

		the most vulnerable children simply do not and cannot participate in clinic patient-based cohorts (31)
	Diversity	more will be learned by funding many different cohorts that represent populations with a variety of geographical, age, gender, racial/ethnic, and socioeconomic characteristics (110)
	Consent	the requirement that consent forms must allow for data sharing across studies will likely require re-consent of participants who consented sometime in the past (50)
	New cohorts or samples	we urge NIH not to adopt a blanket prohibition on developing new cohorts, as such a position may negatively impact the pursuit of meritorious projects where high-quality extant cohorts simply do not exist (156)
		developing a core data collection protocol is worthwhile, but the primary focus should be developing a protocol for use in new cohort studies (88)
Other	each cohort has its unique features, and thus flexibility should be given to each cohort and cohort-specific data collection should be encouraged (165)	
Biological samples	Existing specimens	many existing pediatric cohorts did not and do not collect maternal or perinatal data. While this data could be pursued retroactively, doing so would likely be both difficult and unreliable since much of the information would depend on parental recall and transient but critical environmental exposures, sometimes many years after the fact (44)
		some extant cohorts have shortcomings: for example, previously biobanked specimens may not include blood or tissue for chemical or biological analysis, necessitating a potentially expensive add-on component (92)
	Other	questions as simple as which tissue to analyze from pregnancy (e.g., placenta, cord blood) will require careful consideration (98)
Opportunities	Exposures	given the fact that a child's first environmental exposure is in utero, [respondent] continues to encourage NIH to place an emphasis on pregnancy and on the intra-uterine environment (182)
		nutrients should be among the biological and chemical environmental factors influencing all four focus areas, and not just as variables affecting obesity (126)
		there appears to be no focus on paternal factors (e.g., chemical, social, physical) or the mechanisms by which they may impact offspring health and development (e.g., sperm epigenetics) (82)
		measuring factors such as urban blight, neighborhood cohesion, physical disorder, physical decay, street safety, residential mobility and concentrated disadvantage could be very important and their long term impact on child violence, maltreatment, and injuries would be very important (151)
		we strongly recommend inclusion of alcohol, nicotine, heavy metals, illicit drugs, and pharmaceutical agents with known or suspected teratogenic potential (128)
	Diseases or conditions	it may also be important to explicitly include a mention of environmental factors that contribute to resilience and enhanced social/behavioral and intellectual/cognitive development and functioning to complement the focus on impairment in these areas (139)

		description/quantification of chronic comorbid conditions (acquisition and maintenance (73)
		we encourage you to consider the relationship between eczema, asthma and allergies, commonly referred to as the atopic march (60)
	Scope	in addition to the areas already identified, we would suggest that emphasis be placed on biological factors that may act as mechanisms for a range of diseases and disorders that transcend medical and academic discipline (87)
		although the core elements include “psychosocial environment,” that terminology is generally used narrowly and does not include major social environmental issues such as social structure, discrimination, family instability, intergenerational patterns of economic disadvantage, immigration, residential segregation, etc... (168)
		integration of basic science within ECHO is paramount to ensure that mechanistic and epidemiologic approaches synergize and capitalize on data and biospecimens gathered from the project (92)
	Other	there is a need to evaluate the health impacts of local, regional, and national climate change policies on children’s health, particularly taking into account equity across populations (106)
Existing resources	Cohorts	The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) established the “Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b)” in 2009... The Network enrolled and followed over 10,000 racially, ethnically, and geographically diverse women from early pregnancy through delivery (enrollment 10/2010–9/2013; last delivery 5/2014). The study included collection of socio-demographic factors (including residential address at four time points during pregnancy for geocoding); maternal nutritional, behavioral, and psychosocial assessments; clinical and sonographic measures; maternal and neonatal outcomes; and maternal, fetal, and placental specimens... To date, over 5200 women have participated in 6-month interval contacts via telephone interviews or online questionnaires; over 1500 eligible women have attended clinic visits; and approximately 450 eligible women have had sleep studies following the clinic visits. Follow-up of the children from the nuMoM2b cohort is an opportunity for the ECHO Program to leverage the richly characterized phenotype of these children’s initial environments beginning in early pregnancy; and the ongoing interval contacts with the mothers allows for easy-access to the children as a whole and for targeted substudies. Furthermore, the materials and systems are available for further enrollment to nuMoM2b (for example, through IDeA state centers), if needed, to increase cohort membership or to enhance diversity. (134)
	Sources of information	one ready source of data is electronic health records (EHRs). Adoption of EHRs has accelerated over the past decade and now exceeds 75 percent in both acute and ambulatory settings, creating a vast body of clinical data available for clinical research (159)
		remote sensing, wireless mobile technology methods of data collection (4)
	Other	I would suggest looking beyond the US and include cohorts from other countries where there is an existing collaboration with US investigators (127)

IDeA Network proposal	Population	[respondent] endorses the proposed IDeA States National Pediatric Clinical Research Network. With 61% of its population residing in rural areas, Maine is well poised to evaluate health access problems and other health disparities among rural children (142)
	Goals	we support the training of clinical trialists in IDeA states and locations to expand recruitment and engagement of pediatric patients in clinical trials. Simultaneously, we encourage NIH not to limit this activity solely to research institutions located in IDeA states (92)
	Fit with ECHO	rather than launching new cohort or longitudinal studies in IDeA states, ECHO should consider grants to involve pediatric, environmental, and social science researchers in IDeA states in the collection and analysis of new data in extant nationally-representative longitudinal studies (168)
	Other	IDeA states often collaborate with other investigators at different institutions to help supplement expertise and fill gaps not available in the region (170)

Request for Information (RFI): Inviting Comments and Suggestions on the Environmental influences on Child Health Outcomes (ECHO) Program (the National Children's Study Alternative)

Notice Number:
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Key Dates

Release Date: July 12, 2015

Response Date: August 14, 2015

Related Announcements

None

Issued by

National Institutes of Health ([NIH](#))

Purpose

This Notice is a time sensitive Request for Information (RFI) inviting comments and suggestions on the proposed plan for the Environmental influences on Child Health Outcomes (ECHO) program.

NOTE: It is important to read this entire RFI notice to ensure an adequate response is prepared and to have a full understanding of how your response will be utilized.

Background

In 2000, Congress authorized a study of children's health and development the National Children's Study (NCS) as part of the Children's Health Act. Due to concerns of NIH leadership and stakeholders, in June 2014 the Institute of Medicine (IOM) was asked to review the NCS, a proposed national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on child health and development. The resulting IOM report expressed concerns about the study's design, management, oversight structure, and anticipated cost. As an outcome of the IOM report, the launch of the Main Study for the NCS was put on hold, and a working group of the Advisory Committee to the Director (ACD) of NIH, which included experts in the fields of pediatric and environmental health, was charged with reviewing the NCS to evaluate its feasibility. In December 2014, the ACD recommended that, while the overall goals of the NCS should remain a priority for future scientific support, the NCS was not feasible as currently outlined. After careful consideration and discussion with NIH senior leadership, Dr. Collins accepted the ACD's recommendation to discontinue the NCS.

To make best use of fiscal year (FY) 2015 appropriated funds, NIH leadership and staff worked diligently to identify opportunities to address challenges at the intersection of pediatric and environmental health through alternative approaches that are consistent with the original goals of the NCS, including establishing compelling new programs, integrating existing programs, and enhancing programs by incorporating more comprehensive environmental assessments. A major focus of the comprehensive effort is on the development of tools to enhance measurement of environmental exposures (e.g., physical, chemical, biological, psychosocial) and facilitate research across all of the initiatives and programs. Another key component of the plan is studying environmental influence on placental and in utero development, with the goal of identifying the "seeds" of future diseases and conditions. Finally, by leveraging extant programs, the plan aims to expand examination of environmental influences on later child development. In keeping with the spirit of the NCS, these initiatives aim to address the critical goal of understanding the impact of environmental influences on children's health and development to advance the field and our knowledge.

Going forward, the overarching goal of the FY 2016 plan is to leverage and expand extant cohorts to address new research questions to investigate the longitudinal impact of prenatal, perinatal, and postnatal environmental exposures on pediatric health outcomes with high public health impact. To do so, NIH proposes to support multiple synergistic, longitudinal studies using extant cohorts that represent variable environmental exposures (e.g., physical, chemical, biological, psychosocial, natural and built environments) that will share standardized research questions and focus on four key pediatric outcomes. All longitudinal studies will collect the same standardized, targeted data (Core Elements) as a component of the project, and will be managed through a Coordinating Center. The Coordinating Center, which will include an analytical or data science component, will be supported through a cooperative agreement with NIH. It will be overseen by a Steering Committee with NIH staff, the heads of the Coordinating Center, and the PIs of the studies.

- The Core Elements to be addressed across all studies:
 - Demographics [e.g., race, gender, ethnicity, socioeconomic status, geographic location/diversity (e.g., IDeA States)]
 - Typical early development [e.g., growth, milestones, microbiome, sleep, nutrition, activity level]
 - Epigenetic influences on early childhood development [e.g., maternal "exposome"]
 - Environmental factors [e.g., physical, chemical, biological (in utero), psychosocial, natural and built environments]

- Four focus areas will address research questions specific to critical pediatric conditions or health outcomes to assess range of functioning over time. These Focus Areas are:
 - Upper and lower airway (e.g., asthma, allergies, sleep disordered breathing)
 - Obesity (e.g., nutrition, diabetes, metabolic risk factors)
 - Pre-, peri-, and postnatal outcomes (e.g., birth defects, childhood outcomes)
 - Neurodevelopment [e.g., autism, ADHD, depression, social/behavioral development, cognition]

The FY 2016 plan aims to provide the flexibility and opportunity to investigate key questions of interest at the intersection of environmental health and pediatric research, while also leveraging additional features and capabilities of the studies. For example, the studies could: take maximal advantage of existing tissue banks collected across pregnancy (e.g., cervicovaginal secretions, maternal DNA, cord blood, placenta) and data sets by funding additional analyses; serve as a test bed for validating new

technologies, tools, and approaches for efficient and effective environmental and pediatric monitoring; use systems approaches to develop multivariable models to predict disease development; recruit future pregnancies and investigate outcomes of second children to serve as a comparison cohort to first pregnancy children.

As an additional research opportunity, the FY16 plan also proposes to create an IDeA States National Pediatric Clinical Research Network, which could:

- Address access gaps for rural children through a national network for pediatric research embedded at IDeA locations
- Link existing IDeA state centers with experts in clinical trials

Information Requested

This RFI seeks input from stakeholders throughout the extramural scientific community and the general public regarding the FY16 ECHO plan.

The NIH seeks comments on any or all of, but not limited to, the following topics:

- The Core Elements:
 - Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements
 - Additional core elements to be considered
 - Considerations for harmonizing data across cohorts
 - High impact areas of opportunity in addition to those listed
 - Anticipated advances and/or considerations for implementing state of the art data collection and analytic methodologies throughout the duration of the study
- The four Focus Areas:
 - Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)
 - The additional IDeA States opportunity

How to Submit a Response

All comments must be submitted electronically on the [submission website](http://grants.nih.gov/grants/rfi/rfi.cfm?ID=45) (<http://grants.nih.gov/grants/rfi/rfi.cfm?ID=45>).

Responses (no longer than 300 words in MS Word or pdf format) must be received by 11:59:59 pm (EST) on August 14, 2015. You will see an electronic confirmation acknowledging receipt of your response.

Responses to this RFI are voluntary. **Do not include any proprietary, classified, confidential, trade secret, or sensitive information in your response.** The responses will be reviewed by NIH staff, and

individual feedback will not be provided to any responder. The Government will use the information submitted in response to this RFI at its discretion. The Government reserves the right to use any submitted information on public NIH websites, in reports, in summaries of the state of the science, in any possible resultant solicitation(s), grant(s), or cooperative agreement(s), or in the development of future funding opportunity announcements.

This RFI is for information and planning purposes only and shall not be construed as a solicitation, grant, or cooperative agreement, or as an obligation on the part of the Federal Government, the NIH, or individual NIH Institutes and Centers. The Government will not pay for the preparation of any information submitted or for the Government's use of such information. No basis for claims against the U.S. Government shall arise as a result of a response to this request for information or from the Government's use of such information.

We look forward to your input and hope that you will share this RFI document with your colleagues.

Inquiries

Please direct all inquiries to:

Email: nihkidsandenvironment@nih.gov

RFI Responses¹

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

There may be very few studies that have: collected such a wide array of domains of "Typical Development"; measured epigenetic marks; or assessed more than a couple of types of environmental exposures. Because utilization of existing pregnancy cohorts necessarily limits the # of common exposures across cohorts, any specific exposure information may only have been collected on a few cohorts. To determine the extent of this problem, and to identify which exposures are common across multiple studies that have also examined some of the same outcomes, it would be incumbent to assess the value and feasibility of this approach. That is, the first step that ought to be taken before embarking on this large undertaking, is to conduct a survey of cohorts that were initiated during the critical prenatal period, which of the specific domains were addressed in the data collection for each of the core demographic domains, each of the areas of typical development (growth, milestones, microbiome, sleep, nutrition, activity level) and at what ages (since it may be difficult to pool sleep patterns at age 1 with sleep patterns at age 5), "epigenetics" (which itself may need more specificity - DNA methylation? histone modifications? other architectural components of DNA, and what platforms were used for these measurements); and finally environmental exposures (physical, neighborhood, specific chemical classes (as metals, persistent organics, organophosphate pesticides, etc., cannot be combined), psychosocial (a broad domain, as parenting skills, social networks, anxiety, mental health are quite different from each other). For NIH to carry out an effective program requires knowing what is feasible with the proposed strategy. A survey to establish the baseline of existing cohorts and what they offer is essential. This information can then be used to determine sample sizes available, and hence power, to address specific hypotheses.

Additional core elements to be considered

might be), while the rarity of autism may make it virtually impossible to study within the framework proposed, or to add substantially to what is already happening with existing studies. In any case, doing a thorough survey of existing studies and what they have measured, using much greater specificity than the four general categories, is the most essential first step. The leaders of this program need to have an objective assessment before launching this endeavor, a full appreciation for what is going to be feasible and what is not -- the latter will need to be openly acknowledged and addressed: Specifically, armed with the survey results, they can make a realistic assessment, and then solicit fresh ideas about further approaches required to address the key hypotheses that will not be amenable to the reliance on extant studies. Example: how many studies, and of what size, measured/assessed PBDEs, pesticides, phthalates along with maternal metabolic conditions during pregnancy (or psychosocial measures, or nutrition) - likely susceptibility factors - and have neurobehavioral outcomes at ages 3-6?

Considerations for harmonizing data across cohorts

The starting point is to understand what is offered by existing cohorts, i.e., how many children from how many cohorts, from which birth years, have the various exposures, demographic features, biologic measurements, typical development assessed, and specific types of environmental exposures? The NICHD team can learn from the EU where an initial survey of multiple pregnancy and birth cohort studies was conducted (Larsen et al, Pregnancy and birthcohort resources in Europe: a large opportunity for aetiological child health research. *Paediatr Perinat Epidemiol.* 2013 Jul;27(4):393-414. doi:

¹ Identifying information has been removed

10.1111/ppe.12060. PubMed PMID: 23772942). This led to a variety of pooled analyses that have now been published, with more underway. A major consideration is the cost and burden on investigators to work through what information is comparable or can be harmonized and what cannot, and then how to do it. It is easy to underestimate the time and effort this takes. Funds must be allocated that will support this process. It can be particularly difficult for studies that are no longer funded or are no longer in the field. Additional consideration should be given to expanding existing cohorts with further recruitment so as to ensure standard methods of collection for priority exposures and outcomes going forward in time. Moreover, the potential to establish new cohorts at institutions that previously developed infrastructure for the NCS should be examined carefully

High impact areas of opportunity in addition to those listed

is fundamental to ensure a strong likelihood of identifying toxic exposures or key protective factors, and for discovering early biomarkers of risk. These types of advances – identifying environmental risk or protective exposures and early biomarkers -- are essential elements of the success of the proposed strategy. In other words, any proposal should be evaluated by the metric of how rapidly the science will lead to interventions that can reduce risks or mitigate the severity of conditions with prenatal origins.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

High throughput technologies for measurements in biospecimens and in environmental samples. These specimens are precious and because there are so many types of analytes of interest, depending on the investigator's discipline and area of inquiry, maximizing what can be obtained in small samples is truly essential. Biorepository support – extant studies find it difficult to maintain their biospecimens after the funding has ended. Few institutions have dedicated the necessary resources to this.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)
(*Submitter left answer blank*)

The additional IDeA States opportunity

(*Submitter left answer blank*)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

We support a broad consideration of the extant cohorts. We believe that international cohorts should be encouraged. Some existing international cohorts present the opportunity to have large study populations with measurements of multiple core elements. Exposures in other countries are often higher in magnitude, yielding greater contrast in exposure groups and enhancing power to detect exposure-outcome associations. These etiologic associations would have relevance to the U.S. population. We believe that a hypothesis-based approach (i.e., rather than a prescriptive cooperative agreement) would be most effective and yield the greatest informative value.

Additional core elements to be considered

We agree with the value and importance of including epigenetic influences on children's health and development. In addition, we support expanded this core element to include evaluation of the genome, epigenome and of gene-environment interactions.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

The timing of puberty has been related to several important future health outcomes including subfecundity and breast cancer. In turn, timing of puberty is an endpoint that is sensitive to both environmental and dietary exposures. Given the focus of the original National Children's Study on environmental exposures and childhood obesity, we suggest that pubertal development, for both male and female children, be added to the list of Focus Areas for this RFA.

Attachments: *(No attachment)*

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Potential Benefits: taking advantage of prior investments in cohort recruitment, dataset and biospecimen collection to extend collaborative studies to related but currently unfunded questions, broadening the populations considered. For example, our cord blood repository, along with PBMC, plasma, urine, nasal/throat and rectal swab specimens and data we've collected from preterm and temporally matched full term infants for the Prematurity and Respiratory Outcomes Program and the Respiratory Pathogens Research Center Projects, could be readily assayed for environmental exposures (ex. triclosan, BPA, and phthalates), reflecting in utero/ maternal as well as postnatal sources, and compared to composition of respiratory and GI microbiome, growth, immune and respiratory function developing over the first 3 years of life. Drawbacks: the opportunity to collect some of the developmental "standardized data elements" will have been missed for established cohorts; definitions

of data elements already collected are likely to vary between studies

Additional core elements to be considered

Gestational age at birth and NICU environmental exposures. Environmental factors affecting in utero growth restriction, pulmonary hypoplasia, preterm delivery

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Prematurity and Respiratory Outcomes Program has been described by Dr. Aschner in reply to this RFI. In addition, we are completing recruitment into a similar study for the DMID Respiratory Pathogens Research Center. Sample Size: 150 infants born prematurely (< 35 6/7 weeks) and 100 full term infants Site: University of Rochester Medical Center Demographics collected through birth hospitalization and then each month for 1 year, with respiratory illnesses during second year and with follow up visit at 3 years: race, gestational age, gender, daily logs of nutrition, growth, medications, respiratory support, respiratory symptoms, history of food and respiratory allergy symptoms Biospecimens collected: Maternal saliva within 1 week of birth, infant and parental DNA samples, Cord blood, discharge, 1 year and 3 year blood samples stored and analyzed as PBMC and plasma by multiplex flow cytometry/ELISA and multiplex protein analyses, respiratory and GI mucosal swabs analyzed for metagenomics/microbiome/virome, Samples remain for further investigation In addition, our cord blood repository continues to grow with isolated PBMC and plasma from preterm and full term deliveries with currently > 1000 samples, consented for research use with access to maternal and infant hospital records. Families for each of these studies are already consented for future contact and future research study approaches. We would be excited to collaborate with other centers and investigators to make additional use of the data and samples generously provided by the children and parents of these cohorts

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Most 'extant' (e.g., existing in 2015) cohorts established to evaluate pre-conception to early-life

exposures and outcomes will have ‘aged-out’ of the exposure windows of greatest interest by the start of ECHO funding. We therefore suggest that the RFA explicitly allow/encourage ‘refreshment’ of cohorts with a new wave of subjects from the source population from which an extant cohort was drawn (e.g., add a new wave of pregnant women to a now extant cohort of pregnant women). This approach capitalizes on the significant extant cohort research infrastructure (e.g., trained staff, field offices, validated methods, etc.) and well-established community relationships. This approach will increase extant cohort sample size, and if necessary, recruitment of the new wave of subjects could be modified slightly to answer key questions arising from analysis of data from the first (extant) wave of subjects.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

To facilitate harmonization, we suggest that the NIH create a website ‘clearinghouse’ of information (e.g., a matrix) on current studies, detailing the following: study population, health outcomes, exposures, protocols, validated instruments in use, and contact information for, as well as willingness of each project’s PI, to share additional information and/or collaborate directly. NIH staff could create a matrix to which investigators could add/correct/update information.

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Children’s Health and Air Pollution in the San Joaquin Valley (CHAPS-SJV) is the Berkeley-Stanford Children’s Environmental Health Center. Several studies currently exist within CHAPS-SJV, one set focusing on birth outcomes while another set is recruiting three cohorts and examining atopy, immune function, obesity/glucose dysregulation and pulmonary function. All focus on children and air pollution (criteria pollutants, PAHs, and black and brown carbon); individual exposures are estimated daily. CHAPS-SJV is studying two birth outcomes, birth defects and preterm birth. The birth defects study uses data from an 8-county area derived from the population-based case-control National Birth Defects Prevention Study (NBDPS). Interview data and DNA samples (buccal from mother, newborn bloodspots from baby) are available for approximately 4500 birth defect case and 1400 control mothers. The preterm birth study is in a 4-county area with data derived from California birth certificates. No biologic specimens are available for this study. CHAPS-SJV is recruiting and following three cohorts (primarily low-income and Hispanic) from Fresno with high potential for continued follow-up. Health outcomes include atopy, immune function, pulmonary function, and obesity/glucose dysregulation, and data collected include blood, urine, and buccal specimens, questionnaire data, and anthropometry. The three cohorts are: 1. Pregnancy/Newborn cohort: 220 pregnant women and their babies. Data collection at 18-25 weeks gestation, birth, and when child is 1 and 2 years old, 2. Child cohort: 220 7 year olds. Data collection twice, at 7 and 9. 3. Adolescent/Young Adult cohort: Re-recruitment of 200 former

participants in two prior studies in Fresno: The first, FACES, recruited 315 asthmatic children (6-11) in 2000-2006 and examined acute response to air pollution and longitudinal changes in lung function. The second, the CHAPS pre-center, recruited 403 children (half asthmatics) in 2010-2013 and measured immune function and pulmonary function; blood samples were collected.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Benefits relate to cost and time savings. Drawbacks depend on the types of cohorts chosen. If all ECHO cohorts cover similar contemporary births with no ancestral data, the opportunity to understand multi-generational effects will be lost. The desire for harmonization of data items could drive ECHO to a form of homogeneity that will stifle discovery. This is much like looking for your keys only on the north side of the street when they are on the south side. There are many dimensions that should be covered even when harmonization is imperfect. This might be accomplished with special purpose study arms. See comments below on designing a multi-generational arm. Too much emphasis on harmonization could stagnate the study. Pick innovative investigators who care about data quality as much as they care about anything. Share, but do not hamstring their efforts. Use the experience of investigators that have maintained long-term pregnancy cohorts to advise you on methods and study populations that are likely to remain under observation. Some settings are better than others.

Additional core elements to be considered

1. Trans-disciplinary teams need to be supported and nurtured to make ECHO a success. This should happen at the very outset of the program by offering incentives to integrate basic science, socio-biology, developmental biology, toxicology, biochemistry, genomics, epigenomics, metabolomics, and a strong statistics and bioinformatics team. Effort should be made to recruit innovators as there is likely less to be learned from business as usual. Money should be set aside to find and fund state of the art-omics methods. These teams should be made available to all ECHO collaborators-- perhaps independently supported as cores.. 2. Any study of pregnancy is out of date the day after it starts... the exposures of today will not be the exposures of tomorrow--literally. For this reason, it is not new to start ECHO -- there have been other large pregnancy cohort studies before. 3. What would be new--- is to run ECHO in study populations where multi-generational exposures can be measured --really well quantified-- internal dose quantified in sizeable populations during critical developmental windows. This should be a required feature of at least some aspect of ECHO (see below).

Considerations for harmonizing data across cohorts

See first comment field. In addition, what is most important is planning for and implementing a plan for collecting new biospecimens including their storage... (e.g--specimens, aliquot size, placenta, and storage methods) Choose cohorts with dense and meaningful data on great grandparents, grandparents ,parents of ECHO children (see last comment box)

High impact areas of opportunity in addition to those listed

ECHO OPPORTUNITY for MULTI-GENERATIONAL and TRANS-GENERATIONAL RESEARCH The re-design of the children's health study provides a unique opportunity to build an unprecedented multi-generation study arm. Consideration should be given to the benefits of recruiting pregnancies and young children of women who are known descendants of well-characterized PREGNANCY cohorts, with available archived bio-specimens in ancestral generations collected during development-- ie during a founding pregnancy or at pre-conception. The goal is to observe a minimum of three generations (F0, F1, F2) for the parental line, and four generations (F0, F1, F2, F3) for the parental line as is required to determine whether trans-generational effects occur in humans and to observe interaction between ancestral and current environments during developmentally sensitive periods. Preferentially enrolling F2 and/or F3 about to be born should be a priority of one arm of ECHO. The benefits of this strategy are: 1) As for other ECHO populations that might lack ancestral data, contemporary pregnancies (and contemporary young children) can be followed. 2) The history of prior developmental exposures, during critical windows of susceptibility can be studied as well, including the shared in utero exposure of fetus (F1) and germline (F2), and its potential consequences for F3. The demonstration of clear trans-generational effects in animal studies make it imperative to have human data for proof of concept for trans-generational inheritance of environmental insults in humans. If we do not create a multigenerational ECHO study arm, it will take a waiting period of at least 50 years to recover the opportunity for this critical work. The typical NIH opportunities do not provide a true opportunity to make this happen. ECHO can play a critical role.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

ECHO should not invest greatly in expensive and untested external environmental monitoring. Instead biospecimens that record internal dose and response are a better investment as these can be archived awaiting the new technologies to come. External monitoring cannot show us the response of the individual to the exposure. So if funds are limited, go for INTERNAL DOSE and biospecimens that can measure this and also response. Investment in data bases that enhance collaboration, quality control of existing and ongoing data items--even if these are not identical across cohorts, and methods/approaches for communicating with cohort members, retaining them, and for encouraging/demanding cooperative behavior of collaborators is a good investment. A strong Director of each ECHO study population who is committed to development of the resource and not solely to their own research and career advancement is critical.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

Child Health and Development Studies (CHDS) is a 50+ year follow-up of 20,000 pregnancies with demonstrated ability to contact original families and their descendants and enroll them in new studies. The serum archive includes specimens from the original fathers (F0m) and mothers (F0f) during pregnancy. Medical records and interview data for the founding pregnancies are extensive.

Contemporary biospecimens have also recently been collected from a subset of F0 females, F1 females and their daughters (F2 females), and from F1 males, including a successful semen study. The F0 (in their 70's) are an excellent cohort to study the early life risk factors of dementia frailty and chronic disease. The F1 (in their 50s) are an excellent cohort for investigating the impact of pregnancy exposures in utero over their life-course to date, including extensive data on health and growth in infancy and childhood,

with the ability to begin new prospective observations now in their mid-life. The F2 are an average age of 18, with some already parents. These F2 pregnancies and F3 infants and children could form the first trans-generational human cohort ECHO should allocate funds to collect data on the pregnancies and offspring (F3) of these very unique CHDS F2 women and men of reproductive age. The sensitivity of many biological systems to perturbations in early development has been shown in animals, as has the potential for trans-generational effects. The CHDS is one of the only resources to form a human trans-generational study now, without waiting another 50 years. This opportunity should not be missed as these data are a National Treasure.

The additional IDeA States opportunity

See above... Fund the CHDS as a National Resource for understanding the impact of environmental insults on the fetus and germline, and the relation of these effects across the life-course for men and women over four generations. DO NOT ABANDON THE OPPORTUNITY TO COLLECT DATA ON THE ECHO MOTHERS AND FATHERS-- young adulthood carries risk for midlife and old age. For women, pregnancy is a critical exposure period for the development of cancer and heart disease. For example, in addition to studying the relation of quantified in utero environmental exposure to cancer in CHDS F1, CHDS is about to publish an important paper in *Circulation* on the relation of pregnancy response to prediction of early cardiovascular disease death. NIH investment in ECHO can yield many benefits... We care about children, but also about the men and women they become.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Leveraging the current NICHD Networks, such as the MFMU and NuMoM2B, provides several advantages including the convenience and economics of preexisting cohorts of pregnant women. Other benefits include the opportunity for prolonged evaluation periods to ensure sufficient follow-up to assess a wider variety of outcomes. Prospective data collection for the existing cohorts is rigorous, standardized and comprehensive which would strengthen the overall evaluations of risk and protective factors and outcomes in ways that cannot be accomplished by administrative or retrospective data collection. The NIEHS/EPA Children's Center data could be utilized as well, as it specifically looks at prenatal exposures and provides an existing structure to leverage.

Additional core elements to be considered

A survey of [respondent] membership shows that more members prioritized environmental factors as the most important core element for inclusion. We urge NICHD to emphasize the intrauterine environment within this core element. The life course perspective provides an important framework for understanding the totality of risk factors and protective factors. This perspective clearly has intrauterine origins—the intrauterine environment is the first environment to which the child is exposed.

Considerations for harmonizing data across cohorts

By including existing NICHD networks, the majority of the data elements would have been harmonized. In addition, the previous NCS has already harmonized a large data set. For other cohorts, it would be important to have consensus from experts in the field to harmonize data. Specific to harmonizing data, we encourage the NIH to use the reVITALIZE data definition standardization efforts underway by ACOG

and others to harmonize definitions of data elements used in obstetrics and gynecology. These efforts will surely assist in the harmonization of data in the future as it relates to women and newborns.

High impact areas of opportunity in addition to those listed

The areas of greatest opportunity today to reduce morbidity and mortality and diminish racial disparities in health outcomes include obesity and cardiovascular disease. Increasing evidence points to intrauterine origins of these prevalent adult diseases and an opportunity for primary prevention to reduce the burden of these health conditions. [Respondent] encourages NICHD to emphasize study of the effects of the intrauterine environment by including maternal-child cohorts in ECHO to provide an all-encompassing look at child development and new opportunities for intervention. Given the fact that a child's first environmental exposure is in utero, [respondent] continues to encourage NIH to place an emphasis on pregnancy and on the intra-uterine environment. Including maternal-child cohorts in ECHO will provide a long-term all encompassing look at child development. This is surely of the highest impact.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

3D evaluation of the placenta and imaging of the fetus during pregnancy, with storage of the images for future analysis are extremely important innovations that should be utilized for the study.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

[Respondent] encourages NIH to consider the inclusion or linkage of existing maternal-child health networks in its plan for FY2016 and beyond.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

On behalf of [respondent], we applaud the National Institutes of Health's continued focus on children's environmental health through the ECHO program. One of the opportunities that the ECHO challenge provides is a window to look at several important scientific and methodological challenges associated with Children's Health Cohorts. We have summarized our key concerns and comments regarding the ECHO study below: 1. Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements We applaud the continued focus on children's environmental health, but ask for flexibility on data collection to facilitate inclusion of more relevant and diverse cohorts. The ECHO program will leverage existing cohort infrastructure to build synthetic cohorts. However, if the synthetic cohort requirements are too rigid, important diversity in lifestage, exposure assessment and outcomes may be lost. Limiting the synthetic cohorts by lifestage will significantly reduce the number of eligible cohorts and unintentionally narrow the capacity of the study.

We would ask that you consider ensuring that we have the option to include developmental cohorts across life stages.

Additional core elements to be considered

2. Additional core elements to be considered We strongly encourage equal emphasis on exposure and outcome assessment. The Children’s Health Act of 2000 charges scientists to address the gap in information needed to conduct full risk assessments of children’s health by “evaluating the effects of both chronic and intermittent exposures on child health and human development” and investigating the “basic mechanisms of developmental disorders and environmental factors, both risk and protective, that influence health and developmental processes”. This has driven the study of broad-based environmental factors including physical, chemical, psychosocial, behavioral, and education on children’s wellbeing and development. As the field of children’s environmental health risk assessment moves forward, we need to understand the cumulative impacts of exposure to multiple environmental contaminants, genetics, lifestage and other susceptibility factors. In order to understand how gene by environment by time relationships that influence children’s health and wellbeing, it is important to characterize cumulative exposures. Because children are exposed to a host of environmental contaminants, the concept of the exposome is particularly relevant to children’s environmental health. In the eight years since the term “exposome” was first coined [1], the idea of a measurable, overarching system of exposures has been discussed extensively among scientists. That dialog includes appeals for a comprehensive attempt at measuring the exposome to understand the etiology of chronic disease [2-4]. We emphasize the importance of well-conducted and detailed exposure assessments in the synthetic cohorts of ECHO.

Considerations for harmonizing data across cohorts

We encourage ECHO not to dismiss the data collected from the NCS vanguard study sites. Much of the methodologies developed in the vanguard study can be applied to other longitudinal studies of children’s environmental health[5]. These environmental assessment methodologies have been screened for cost-effectiveness, feasibility and acceptable. It is important that ECHO build on the products of the NCS rather than duplicate efforts. The dataset being established for the Vanguard studies could prove to be very useful in answering many of the questions that arise from Children’s Health Act and which could contribute with focused assessment s. We emphasize the need for generalization that comes from probability based sampling frames. The NCS worked on these aspects and had some successes in setting up and collecting data with birth cohorts established in this manner. For example the EHBR cohorts represent such efforts some with more or less exposure data and some with more or less robust recruitment and some with more or less outcome data. We would encourage plans for ECHO that could utilize these samples, biospecimens and data for addressing key questions from the Children’s Health Act. One could imagine focused targeted studies using these cohorts to answer our challenging questions for Children but which would not require full restoration of the study infrastructure. We encourage ECHO to exercise caution when conducting integrated analysis of exposure and effect metadata. The synthetic cohort approach proposed by ECHO will require a strong framework for integration. This framework must be cognizant of the limitations of this approach. Even at a minimum, establishing a list of cohorts that could be used for answering questions on Exposure and Genes for Children’s studies would be a fantastic resource.

High impact areas of opportunity in addition to those listed

Please note that there are cohorts available that have initially emphasized exposure and early markers of response but which maybe useful in addressing the challenges presented by the Children's Health Act of 2000 by added in an additional outcome measure to link across cohorts and to potentially provide extrapolation of exposure concerns for expanded health outcomes.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

See comments above

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

There are many benefits to leveraging existing cohorts to collect standardized data elements. One major benefit is that many existing cohorts are longitudinal in nature, thus using this opportunity to build on these existing cohorts, containing often extensive and detailed data collection over many years will strengthen any additional data collected. A second benefit is that some existing cohorts may be specialized thus enabling more nuanced questions to be addressed. For example, the Early Growth and Development Study (EGDS), a study that has been supported by NICHD and a number of other NIH institutes, is a longitudinal study of adopted children placed at birth with genetically unrelated adoptive parents. In addition to assessing the adopted children and the adoptive families approximately annually from 9 months to 11 years, birth mothers and birth fathers have also been followed longitudinally across the same time span. Detailed data on prenatal risks, including medical records and birth mother substance use and stress during pregnancy have also been collected. The Early Growth and Development Study permits the interrelations among genetic influences, prenatal environment, and postnatal environment to be examined within a longitudinal study from infancy through adolescence. This is a very rich resource that would be very expensive and time consuming to initiate independently. There are a number of examples of existing cohorts that have unique characteristics that should be leveraged.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

Data harmonization is complex, but is generally achievable. A number of studies currently underway and with published reports have successfully harmonized data across many data sets. For example, the Psychiatric Genetics Consortium are harmonizing data sets across many different countries using wide variety of assessment strategies. To date their published work has been high successful.

High impact areas of opportunity in addition to those listed

Prenatal influences are increasingly being identified as conduits through which genetic risks exert their influence on child development. Understanding how genetic risks may increase prenatal risks on children and under which circumstances these risks are most likely to be manifest is of critical importance to advancing our understanding of child development and for designing strategies to prevent these risks from impacting child functioning. Specialized samples will be required to rigorously disentangle these factors.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Early Growth and Development Study (EGDS; Leve et al., 2013, TRHG) is a prospective, longitudinal parent-offspring adoption study that has followed adopted children, their adoptive parents and the birth mothers and fathers from the child's age of 3 months to 11 years. All study participants have been followed longitudinally and a cohort of siblings of the adopted children who are being reared by their biological parents has also been assessed during middle childhood. A total of 516 sets of adoptive family-birth parents comprise EGDS. The EGDS has helped to clarify that genotype x environment interactions occur during infancy and throughout childhood and findings have suggested that even relatively subtle disruptions in the rearing environment may have a profound effect on the behavioral development of a child at genetic risk.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

The idea of leveraging cohorts is an excellent and cost effective opportunity to advance the science. Among existing cohorts, there should be an emphasis in two distinct areas. First, an emphasis on nationally representative samples, or at least samples with many different geographic locations. This is important for having high levels of contrast in both the physical and social environment, as well as subsequent biological differences. Within cohorts that are too geographically constrained, many of the most interesting contrasts in geographic health differences in the United States will be out of the range of understanding. The second area is focusing on the offspring of well characterized cohort studies. Many of the outcomes and exposures are likely to be confounded by both social and biological characteristics of the parents, so detailed measures of these factors will allow for better inference in the offspring. Within all of these decisions, it is critical that population health scientists who have expertise in causal inference from observational data play a key role. Some of these potential cohorts could include those used more frequently by social scientists.

Additional core elements to be considered

The core elements are missing a specific focus on the social environment. This domain has been demonstrated to have as high or higher level of correlation with the outcomes under focus. Other domains, such as epigenetic, can't be fully understood without good measurements of the social domain.

Considerations for harmonizing data across cohorts

Cohorts that have oversampled or are primarily in low income communities and racial and ethnic minority communities should be prioritized to allow accurate imputation for data harmonization within these groups. It is key that individuals with expertise in survey sampling are included so that with harmonization the final analytic datasets can be used with weights that would make estimates match those of the U.S. Census derived population - to be nationally representative. Data sharing, full access for all scientists to all of the data, must be an essential element of all of the incorporated studies.

High impact areas of opportunity in addition to those listed

Large intervention trials of environmental, structural and behavioral interventions are important to include so that there can be better causal inference about what specific actions may benefit child health.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

A major benefit of leveraging existing cohorts of children whose mothers were recruited pregnancy is the availability of prenatal exposure data. The in-utero environment has been shown to be one of the most critical determinants of child and adulthood development and health.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Eunice Kennedy Shriver NICHD MFMU Network is a well established group of clinical centers and a coordinating center conducting trials and observational studies in pregnant women. Prenatal and pregnancy outcome data are collected with consistent definitions across studies by trained research personnel, resulting in very well characterized and consistently defined prenatal exposures. For all of the studies, women are asked for permission to contact them for future research. The Network has considerable experience in conducting follow-up studies on the children from the studies, both pre-planned and those not initiated until after the completion of the main study. Follow-up rates have been excellent (for example 93% at 5 years for one study), although the population is diverse with approximately one-third Hispanic and one-third African American. There are several cohorts that may be of interest, including the following one. The MFMU is presently undertaking a trial to determine whether labor induction at 39 weeks for uncomplicated, nulliparous women with a singleton gestation reduces the frequency of 1) adverse perinatal outcome (including perinatal death, hypoxic ischemic encephalopathy and other severe perinatal complications) and 2) cesarean delivery. In this trial 6000 women will be randomized to either labor induction at 39 weeks or expectant management until 40 weeks 5 days unless an indication arises earlier. The trial started in 2014 and recruitment will be complete in 2-years at the most; thus this represents a potential cohort of healthy very young children and infants. It is proposed that neurodevelopmental follow-up be conducted, including Bayley Scales of Infant Development or IQ (WPPSI), and autism (Social Responsiveness Scale) depending on the age at follow-up.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

I think its a great idea, as most of the cohorts have been put together to ask a key question, and for many of the cohorts the duration of the cohort study may not allow a full understanding of how long the effect lasts. The opportunity to pool more control groups will also be an important benefit. Key concerns

are providing enough funds to adequately collect standardized DNA elements and to be flexible enough to still include cohorts that might not be able for one reason or another to collect all the core elements. The opportunity to better understand how in utero exposures influences subsequent health from birth to childhood will be of great benefit. Another bonus of this approach of studying existing cohorts is that many of these will be interventional which will help with hypothesis testing of underlying mechanisms.

Additional core elements to be considered

It adds expense, but biological samples are critical especially for hypothesis testing and generation. These should include hair, urine and buccal swabs for sure, and for ages where it is no longer incredibly difficult, blood samples. Blood samples should also be collected from mother and father where available. Collection should be flexible and subjects\guardians unwilling to provide 1 or more of the samples should not be excluded. Capacity for epigenetic and genetic analysis is critical. Buccal swabs will allow for epigenetic analysis over time, Blood will provide DNA for SNP analysis. Samples could be banked for future analysis as budgets, technologies permit and when there are appropriate scientific questions to be answered. I think it is also worth performing spirometry on children over 8. The technique is simple enough and the equipment now cheap enough that this could be a core element. Likewise blood pressure would also be a useful and simple addition.

Considerations for harmonizing data across cohorts

I am not a statistician, so my concerns tend more to not making the harmonization requirements to onerous. Obviously standardization is critical, but some flexibility must be preserved. A mechanism to deal with, and take advantage of, the multiple different interventions these studies will include is crucial as looking at interventions designed for one outcome is likely to have surprising and very informative information for other outcomes.

High impact areas of opportunity in addition to those listed

I think an excellent job of initial identification of high impact areas has been done. The biggest areas I see not listed are cardiovascular disease and COPD, though I recognize these are late onset diseases. But as described in core elements some data such as spirometry and blood pressure can still be collected that might be predictive of eventual outcomes.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

As discussed above it is worth collecting blood and cheek swabs as DNA analysis prices will only continue to plummet.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

While this is of course self-serving, the study area of development of lung disease and pulmonary function in offspring of pregnant smokers that I am involved in together with Dr. Cindy McEvoy of OHSU is extremely important in terms of asthma development as children, effects on cognitive development, and early markers of increased risk of COPD and potentially increased risk of cardiovascular disease. Our cohorts together include about 400 moms and 400 babies. There are also other cohorts of offspring of smokers that could be included as well. We have collected the DNA and hair samples I have recommended above and will be following pulmonary function together with pulmonary health

questionnaires. We also have groups with the intervention of supplemental vitamin C during pregnancy. We are not at present, nor have previously collected samples for microbiome analysis, or indices of CNS development.

The additional IDeA States opportunity

I am not qualified to comment.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Considerable benefit is anticipated from re-engaging extant NCS cohorts. For example, the PBS Cohort comprises data from 3 centers on socioeconomic status (SES) and pregnancy histories that may permit selection of sub-cohorts to explore the association between specific prenatal exposures and outcomes in specific ECHO focus areas. Re-engaging extant cohorts will decrease the burden of recruitment, lower cost, and enhance retention. Leveraging cohorts from NCS Formative Research Studies (FRS) may also help the pursuit and exploration of the focus areas. These FRS cohorts/data could generate new prospective hypothesis-testing studies, e.g. using the Worcester County Parental Mental Health FRS one could explore the relationship between parental psychopathology and the onset of newborn, infant, and early childhood behavioral and mental health outcomes. However, there are two major drawbacks we see to using existing cohorts: one conceptual, one practical. Firstly, despite an expanded concept of “environment” in theory, in practice the original NCS focused on classical epidemiologic measures that shaped and limited data collection for extant cohorts. Secondly, and related to the first, with the exception of SES data that are available, most if not all of the other three ECHO Core Data Elements – early development metrics, epigenetic data, and expanded environmental factors - were not systematically collected pre-, peri- and post-natally as part of a standard experimental design for extant NCS cohorts. Thus, existing information on the exposome and its related epigenome is generally lacking to meet ECHO research goals. While sub-groups of a few existing cohorts may help illuminate some key aspects, the majority will not and the scope of these aspects is very limited. Another drawback may be related to an ‘erosion of trust’ and the inability to re-engage existing cohorts that have been through several transitions since their inclusion and release from past NCS activities.

Additional core elements to be considered

Stronger emphasis on systems-based health models and integrative design, data collection, analysis and interpretation would be desirable and timely. Two of the ECHO Core Elements are epigenetic influences and environmental risk factors, but this can be expanded and made more integrative. The emerging field of Molecular Pathological Epidemiology (MPE) looks at how the interplay of genetic, environmental/exposomic and epigenetic factors manifest at the molecular level to contribute to the etiology and onset of diseases across populations. MPE can be employed as an integrative approach to look at both neoplastic (e.g. cancers) and non-neoplastic diseases (e.g. inflammatory or endocrine diseases) in children. Another relevant emerging field is Chromosomal Biology, e.g. how telomere length influences multiple disease states beyond cancer and aging. Maternal and child chromosome data could be readily derived from bio-specimens. However, as mentioned above, ECHO needs to be biology-environment integrative and therefore investigate how the exposome of each individual - and also shared exposomic aspects among families and subpopulations - may influence chromosome biology and health outcomes. Coupled with the “unique disease principle” of exposomics/epigenetics (each person’s

profile is unique) is the idea that “where a person lives really matters”; differences in residential location of just a few city blocks has been shown to strongly influence health physical and mental outcomes in children and adults. Thus, two other areas that should be considered as part of the integrated ECHO health model are: a) narrative and qualitative data – oral and video histories that capture nuanced, contextual aspects of a person’s life and health missed by conventional metrics; b) spatial analytics – the use of GIS to characterize the exposome: most physical, chemical, psychosocial, natural and built environment data are spatially explicit. Where individual spend their time, and activities they do can be captured and analyzed with GIS.

Considerations for harmonizing data across cohorts

Having a well-established, scientifically sound and solid platform for data collection and management, and minimizing protocol changes in the midst of data collection will be crucial to successful data collection. That said, the platform should also not be set in stone, and be adaptive as new knowledge is acquired during the course of the research over several years. The combination of the following two ECHO design principles is highly desirable to create the requisite targeted-yet-adaptive platform, to maximize learning, scientific discovery and cost-effectiveness/efficiency: a) Soundness and Standardization - begin with known and agreed-upon priority health issues, research questions and/or hypotheses (the four Focus Areas are a good start); b) Adaptability - each year or two, consider revising data-gathering design based on discovered knowledge and/or emerging research by others, always informed by ECHO Design 1.0. The networking together of ECHO Sites for coordinated effort and maximal shared learning is also highly desirable, and is evidenced by the proposed IDeA Pediatric Clinical Research Network. The degree to which data are harmonized will depend on the aforementioned targeted-yet-adaptive platform design, and necessary feedback to facilitate communication and sharing of experiences and knowledge. The original NCS advanced operations for data collection by exploring alternative processes and software. Harmonization assumes a fixed form of all data fields accompanied by a data dictionary. Data collection and management could be best served by centralization or reorganization. Data capture and management could be well-served by use of the same software like REDCAP across all study sites that would be transferred in real time from tablets and other hardware products in a FISMA compliant manner. Capture and management software ideally would include functions for validation of receipt of data in a correct format, scheduling, real time querying at the centralized coordinating center, analytic files, exporting and reporting abilities.

High impact areas of opportunity in addition to those listed

In addition to the proposed ECHO foci, it is worth considering an explicit emphasis on minority health and health disparities (the focus of NIMHD) in these outcomes. Significantly higher rates of prematurity, infant mortality and low birth weight in babies of color have been found to be strongly associated with environmental injustice: conspiring conditions of disproportionate exposure to environmental stress and low socio-economic adaptive capacity that render individuals, families and communities vulnerable to burdensome morbidity and premature mortality. Another high impact area would be substance abuse exposure among mothers and their children, and the relationships with expanded notions of environment/exposome. Currently substance abuse in the U.S. is epidemic in scale. Its adverse effects are multidimensional in nature ranging from biological effect on in-utero development to interrupting personal, social, including academic biographies. NCS formative research on parental mental health suggests that approximately one in four pregnant women report substance use (alcohol or illicit drug). This is a priority area for NIDA. This could be further explored as productive relationship between institutes to address a growing epidemic in the U.S. The initial ECHO focus on pregnancy and pre-, peri- and post-natal early life stages is appropriate since they are the windows of highest health vulnerability, and strongly influence later life stages. However, ECHO should be set-up to consider the continuum of

child health and development life stages/exposomes since these must be captured in order to better understand three of the four focus areas: airway disease; obesity; neuro-cognitive development. The major challenge for existing programs – like the Children’s Health & Environment Program of NIEHS (P50) – is the coupling of strong biological and environmental monitoring over the pre-birth-to-early adulthood timeframe. This also represents the biggest opportunity for ECHO.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

Earlier arguments for targeted-yet-adaptive, integrative design and integrative methods like MPE and GIS have been made above, are relevant here too. State-of-the-art data collection in many fields of life sciences and environmental sciences involves aspects of technical innovation (like portable, low-cost sensors in smart phones and PDAs), but also rely on complementary social innovation (like social networks and vibrant researcher-community partnerships). Real-time data collection and processing (e.g. of outdoor and indoor PM2.5 levels) using an array of sensors, including those operated by participants and community collaborators, with subsequent uploading to integrative databases and analytical tools like GIS, represent the leading-edge in environmental monitoring, analysis and interpretation. During the NCS, some of us advocated for stronger partnerships with participants as a means to an end: reaching comprehensive research goals. The logic for this approach is twofold: a) engendering a sense of shared ownership with participants maximizes retention over the long term; and b) comprehensive data needs are served by the integration of diverse data gathering modalities for requisite quantitative, qualitative and narrative data at relevant scales: individual, household, community. The suite of data-gathering modalities and data management tools should interface smoothly with each other, and also with statistical analysis (traditional and spatial) software in order to generate efficient results output and interpretation. This would require rigorous data QA/QC procedure; QC/QA procedures for participant-gathered data have been developed and are no longer an impediment. Depending upon the extent and complexity of the data, the approach could be either to review all data fields or alternatively to take a probabilistic, heuristic approach and set a predetermined probability level of assurance. This approach could be akin to quality profiling using Bayes approaches currently use for other health data profiling. From that standpoint, establishing a standardized protocol for site-level data quality control is warranted.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

In addition to the NCS cohorts that were recruited through the five ARS, there were other NCS sponsored studies such as Task Order 7 in Worcester County, MA, the Parental Mental Health study that successfully recruited a cohort of nearly 1200 NCS-like participants. Through PMHS we have cross-sectional mental health screening and substance use and other data on 822 women and 378 partners that were recruited across the whole spectrum of pregnancy including birth/immediate post-partum. The PMHS cohort includes nearly 900 dyads (mother and child) in Worcester County that may be leveraged for the generation of future hypothesis testing studies exploring the relationship between parental psychopathology or psychosocial environment and the onset of newborn, infant, and early childhood behavioral and mental health outcomes. Upon re-consent of available participants, currently available data on Worcester County and additional survey may allow the creation of the prenatal environmental profile of the cohort for longitudinal follow-up. Another Worcester-team non-NCS related project includes The Holliston Health (H2) Project, an ongoing (since 2013) multi-dimensional,

community based participatory research project based in the Town of Holliston, Mass. It is focused on the association between complex environmental chemical exposures – specifically contamination of local groundwater used for drinking water by natural and anthropogenic contaminants, manganese and chlorinated solvents respectively. The endpoints of primary concern are chromosome disorders (Trisomy 18 and 21), single-kidney birth defects, and neuro-cognitive development in babies and young children, and the primary exposure window is pregnancy. H2 exemplifies a network approach by several institutions: Clark University (exposome, groundwater pollution, GIS), Boston University (epidemiology, epigenome, biostatistics, biomonitoring), and WPI (groundwater modeling, water systems, environmental monitoring). H2 represents an integrative, adaptive approach, and partners with affected residents as well as policy makers and regulators to both understand and then address a complex issue to improve public health.

The additional IDeA States opportunity

As mentioned above, smart distributed network structures with centralized coordination are the way of the future for health research, and have been for some time for climate-change research and long-term ecological research (LTER Network). This is driven primarily by the necessity to pool and cross-subsidize resources and information to illuminate inherently complex systems. We welcome the proposal for a fledgling IDeA Network created on this basis, one that can interact easily with the larger parent ECHO Network. Indeed, we strongly suggest the larger ECHO Program be organized on a similar, up-scaled basis. For example, even though Massachusetts is not an IDeA State owing to its relatively abundant resources, it is highly desirable – and geographically efficient - for Massachusetts and Connecticut to interact with the four out of six neighboring New England states that are designated IDeA: Maine, Vermont, New Hampshire and Rhode Island. In this way New England could represent a compelling regional model of cooperation and coordination that could be replicated in other regions of the country.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

The potential use of leveraging existing cohorts depends on making key decisions about the ECHO cohort selection. First, ECHO studies must include population-based, representative cohort samples to permit generalizability of results beyond a clinic or local geographic area. Population-based representative samples allow for understanding child health outcomes in a broad context that are not dependent upon the peculiarities of non-random, convenience samples. Population-based representative cohorts also allow for the study of health disparities across key population subgroups—such as race/ethnicity, gender, and socioeconomic status. Representative cohorts are furthermore critical for understanding genetic influences on child well-being because lack of population diversity in local or non-representative samples truncates environmental variation, and in turn, genetic, epigenetic, transcriptomic, and gene by environment relationships with child outcomes. Second, ECHO needs to consider an array of social science population-based cohorts in its mix. NICHD, in particular, has invested in a number of large, population-based, cohort social science studies over the past 20 years which collect data on childhood environments, health outcomes, child growth, etc. Included among these cohorts is The National Longitudinal Study of Adolescent to Adult Health (Add Health) – a longitudinal study of a nationally representative sample of adolescents (N>20,000) in grades 7-12 in the United States during the 1994-95 school year who have been followed into young adulthood with four follow-up interviews and a fifth in 2016-18 when cohort members will be 32-41 years. Add Health contains

unprecedented environmental, behavioral, psychosocial, biological, and genetic (including GWAS) data from early adolescence into adulthood on a large, nationally representative sample with extensive racial, ethnic, socioeconomic, and geographic diversity. Add Health also collects health and demographic information on the births/children of the Add Health respondents, allowing an understanding of how parental social, environment, socioeconomic, and genetic factors influence the birth and health outcomes of their children.

Additional core elements to be considered

Clearly, the social environment – in a broad sense – needs to be a crucial element in ECHO; at present, the RFI does not indicate this. Children’s health, growth, and development depend upon a multitude of factors that fall under the umbrella of the social environment. Moreover, those social environmental factors change over time and differ across place, so understanding them is both complex and necessitates continuous monitoring and new methodologies of data collection. Social environmental factors can also interact with other determinants of child health (e.g., genetic endowment) to influence health outcomes and health behavior. Key elements of the social environment include parental characteristics, family structure and transitions, exposure to racism, processes of immigration and assimilation, residential context and mobility, school context and mobility, peer context, and more. Large social science cohort studies such as Add Health (as well as the Fragile Families Study, the Child Development Supplement of the Panel Study of Income Dynamics, and the Los Angeles Family and Neighborhood Survey) are best positioned to help the scientific community’s understanding of how the social environment influences children’s health outcomes, as well as how the social environment interacts with biological and genetic factors to influence children’s health.

Considerations for harmonizing data across cohorts

Harmonizing measures across ECHO cohorts could be both a very important and very challenging endeavor. Substantial planning and buy-in is needed. The social scientific community, particularly demographers, has a great deal of expertise in data harmonization. Consider, for example, the post-hoc harmonization of the National Health Interview Survey, called the “Integrated Health Interview Survey.” This project, conducted by the Minnesota Population Center (in collaboration with the National Center for Health Statistics), has resulted in substantial growth in the use of that nationally representative data set to US study health trends across time. Harmonizing measures across ECHO cohorts should also be inclusive of large, population-based representative samples. For example, if a harmonized measure of discrimination against African Americans is added to ECHO cohorts being followed in San Francisco, Seattle, New York, and Miami, the results of using that measure for children’s health could be very different than if it was collected and measured for the nation as a whole. That is, without measuring such concepts in large, national population-based samples, the scientific and policy communities will have no way of knowing whether such results apply to the population as a whole and/or whether key subgroups of the population experience different health impacts as a result of such an exposure.

High impact areas of opportunity in addition to those listed

As mentioned above, the social science based cohorts are very well suited to understand how the social environment interacts with genetic and epigenetic influences to influence children’s health. Moreover, the opportunity to do so using population-based data and to do so across multiple population subgroups is a very high impact area of opportunity. Second, some of the social science cohort studies, such as Add Health, provide a very unique opportunity to study how detailed parental factors (e.g., biological, social, health) influence child health outcomes. Such intergenerational studies, particularly at the population level, are rare. Add Health and a couple of the other social science cohort studies provide very detailed information on parents so that child health outcomes can be studied in an intergenerational context.

Third, it is extremely important that ECHO involves extramural research grants. The extramural grant process helps insure that cutting-edge research questions and approaches are included as a part of the ECHO Program, and the peer review process for such grants helps insure that only the most promising scientific avenues be funded. The inclusion of extramural grants will also help ECHO achieve broader buy-in from the scientific community, so it is not just seen as a closed-shop internal NIH project. Again, the inclusion of the social science community is extremely important in such an extramural grant process, given the social science community's expertise in collecting and disseminating population-based representative data sets on children's health outcomes over the last several decades and use of these social science data by a wide range of social, behavioral, and biomedical scientists.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

Add Health (www.cpc.unc.edu/projects/addhealth) provides a great example of how social, biological (including genetic), intergenerational, and contextual measures can be collected for a very large nationally representative sample of Americans who are being followed across time. The data have also been publicly disseminated, with great care given to the confidentiality of respondents. The data have been very widely utilized—in the social sciences, the medical sciences, and beyond. Add Health has over 10,000 data users around the world who have produced more than 5,500 articles, books, reports, dissertations, and presentations. Over 3,000 peer-reviewed articles have been published in 350 different disciplinary journals and outlets. The innovations include the very rich social, family, peer, and school data there were collected for each adolescent; the biomarker and genetic data collected for all respondents; an embedded genetic sample of 3,000 pairs of adolescents (i.e., twins, full sibs, half-sibs, and adolescents who grew up in the same household); the linkage of birth certificate data to respondents; and health information regarding the children of the Add Health respondents after they give birth. ECHO cohorts could utilize some of the innovations and lessons from Add Health as it plans for the future.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

As mentioned above, NICHD has invested in several longstanding social science, population-based cohort studies on children and adolescents over the past two decades. Add Health is very well suited to fit into the ECHO set of studies, given its very large size, national representation, oversampling of minority groups, inclusion of social and biologic data, and its rich set of contextual (neighborhood, family, peer) measures. The extensive social and physical environmental data—including toxicological and climate measures—combined with genomic data and biological markers of metabolic, cardiovascular, immune, and renal function make the Add Health cohort ideal for understanding multilevel processes underlying health and development in the early life course. Moreover, Add Health can be used in at least two additional ways to enhance the ECHO Program effort: 1) to collect additional information on the children of Add Health respondents (both as they are born and as they grow up)—thus, allowing for the further exploitation of the rich parental information; and 2) to provide an example of a data collection effort that is both population-based and extraordinarily rich across the social, health, and biologic domains.

The additional IDeA States opportunity

The inclusion of ongoing rich, population-based, social science cohort studies such as Add Health provide ECHO with the opportunity to gain great knowledge and expertise at a fraction of the cost it would take to start a new cohort. ECHO should seriously consider the inclusion of such cohort studies as it moves forward.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

[Respondent] appreciates the opportunity to comment on the Suggestions on the Environmental Influences on Child Health Outcomes (ECHO) Program. We are a Society whose mission is to prevent birth defects and disorders of developmental origin through research, education and prevention, and represent a multidisciplinary group of scientists including basic and applied researchers, clinicians, epidemiologists and public health professionals. We offer the following comments: • The original objectives of the Children's Health Act and the National Children's Study (NCS) are still highly relevant and important for the nation, and these objectives should be retained, • The funds originally allocated for the NCS should be repurposed in a manner that will meet those objectives, • The proposed high priority outcomes are consistent with the original objectives of the NCS and the priorities of our Society, • Strong consideration should be given to assembling a "synthetic cohort" that can accomplish these objectives. This cohort could be selected based on specific hypotheses and/or specific disease states with sufficient power to address objectives that require longitudinal follow-up from prior to conception/birth to adulthood. • Consider allowing additional proposals/research using existing cohorts by giving investigators access to some of the infrastructure being created using NCS funds. Consideration should be given to whether existing cohorts can provide samples that were collected at critical and relevant windows of exposure which would allow for assessment at time points known or hypothesized as important for environmental impacts on children. Existing cohorts may be a starting point but additional subjects/study groups may need to be recruited based on exposures of interest. A PDF file containing all of the Teratology Society comments and suggestions is also attached.

Additional core elements to be considered

- Consider other high impact endpoints such as contributors to prematurity, low birth weight and stillbirths.
- Well characterized prenatal exposures are needed to assess long-term health outcomes on children's health.
- Environmental exposures represent only a part of potential teratogenic exposures, so future studies should be inclusive of substances of abuse (including illicit drugs, alcohol, tobacco), prescription medications, and psychosocial factors (poverty, nutrition, access to resources, etc).

Considerations for harmonizing data across cohorts

- Consideration should be given to interpretation of non-probability based sampled cohorts which might not provide a sampling frame robust enough or specific enough to determine how to link with exposure or other measures.

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

- There are other birth defects surveillance networks which might be helpful.
- Although not a focus of this study, information from drug exposures/studies could be helpful.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

This is in response to NOT-OD-15-117. To move forward with the reinvention of the National Children's Health Study will require novel examination of how environmental factors interact with other factors critical to the mechanisms underlying adverse pregnancy outcomes. In this light, we offer introduction to the New England Consortium for Translational Reproductive Research (NECTRR). Our mission is the study of preterm birth as part of the continuum of adverse pregnancy outcomes, and our theoretical framework is that environmental or other exposures from in utero to postnatal, pubertal, peri-implantation and during early pregnancy contribute to adverse pregnancy and may render pregnancy at

high risk for the whole of the woman's reproductive life. The Consortium comprises experienced investigators in areas such as reproductive immunology, high-risk obstetrics, epidemiology, bioinformatics, ultrasound, animal models of abnormal human pregnancy, from institutions such as Harvard, Tufts, Yale, Brown, the University of Vermont and The Jackson Laboratory, who are able to perform in-silico, in-vitro, animal, clinical, translational and population studies to investigate the specific interaction between macro /micronutrition and inflammation in the generation of placental dysfunction, and ensuing abnormal pregnancy. We represent tertiary care and small community hospitals where upwards of 50,000 deliveries are performed each year. In addition, our investigators have contributed to relevant knowledge in several areas including the role played by deficiency in Folate and Vitamin D, as well as obesity, and the role of perinatal inflammation and maternal microbes in child development. Our Consortium represents an important resource in the implementation of the proposed program.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

I like the approach of building on existing cohorts. As many of these cohorts will be beyond the prenatal recruitment stage, a potential drawback will be ensuring that sufficient exposure assessment data are available to do comparative assessments of exposure-outcome relationships. Ensuring diversity of the composition of cohorts will also be a key consideration. While looking at cohorts that proportionally represent the US population composition may make sense on one level, that methodology is likely to result in insufficient sample size to assess many of the populations at greatest risk for both exposure and health outcomes. Native American populations that I work with, for example have diversity within and across tribes that likely would be lost in such an approach. Yet these populations are collocated with numerous environmental exposure sources, especially from the 161,000 abandoned hard rock mines in and adjacent to tribal lands throughout the west. Similar situations will likely occur for other minority populations in the country as well as for rural and other low SES. Exposure characterization based on not only biomonitoring, but on quantification of environmental sources and in-home exposures will be difficult to achieve, and may require revisiting some of those enrolled in cohorts, or reopening recruitment. Yet good characterization that can link exposure to source is critical in addressing risk factors tied to birth and development.

Additional core elements to be considered

Birth outcomes and early developmental assessments are key, but ensuring cohorts that can be followed into the future to assess latent outcomes will be a challenge. Considering the need for long-term follow up in planning and using the longest possible funding cycle to ensure investigators can maximize follow-up is important. Currently no focus on immune function at birth and early life timepoints. Inclusion of these measures affected by many environmental exposures will be key in determining role of exposure in some latent toxicity endpoints. (discussed further below) PERSONAL NOTE: My apologies for lack of detail in my response -- I am happy to discuss any questions as follow-up, but have been working on response to gold-king mine spill for last week and am not thinking or writing clearly. But wanted to get something in by the deadline. J

Considerations for harmonizing data across cohorts

Exposure assessment including biomonitoring (or access to well preserved samples to obtain) and environmental source characterization Availability of prenatal exposure data, as well as background information on mothers and fathers Ability to obtain similar developmental end-points across cohorts Willingness to work with populations re cultural barriers on providing certain data or samples, or on sharing of such. My expertise is in working in tribal communities, and in those communities, barriers may not allow for the data and sample sharing hoped for in the planning. Issues of local IRBs more frequently being developed by individual tribes will need to be respected, and accommodation for tribal well-documented distrust of research respected. This will likely also extend to unwillingness to allow genetic analyses beyond the standard birth screening. While this may limit some of the harmonization, we know so little about birth outcomes and risk factors, and environmental risks in these populations that it is still critical to include tribal cohorts. Support for harmonization of background survey information already collected to identify similarities in questions and build and validate intersection points within different instruments -- i.e. within the survey differences, can it be demonstrated that different forms of questions trigger common responses and can be combined to provide a common dataset. Variation in state methodologies for tracking birth defects differ dramatically, and needs here should be standardized. Period of assessment varies from "at delivery" to "within the first year". Current data are particularly problematic for tribes in our experience both due to understaffing at IHS, small representation in general population, and state-to-state variations in methodology.. Standardization of how birth defects are identified and tracked should be developed centrally and especially considered for cohorts that may be now be going back into medical records to obtain such data.

High impact areas of opportunity in addition to those listed

Building the common cohorts should also allow for assessment of how prenatal exposures impact long-latency end points such as cancer, autoimmunity. In light of these long-latency diseases, the lack of any assessment of immunocompetence or immunosuppression in the endpoints of interest is currently a gap. These fundamental changes could be key in the endpoints of interest, and certainly in the long-term health of the population. In addition, they could provided important data to inform mechanistic investigations. The role of early development of the immune system, immunosurveillance, immunocompetence should be added..

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

Several avenues of personal exposure monitoring are at various stages of development and beta testing. Encouraging their use and supporting their development through parallel funding would help to expand the exposure characterization, even if added at later points in protocol implementation.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

From experience with IHS, I think the addition of specialized resources to supplement pediatric care

would be a great addition. The limitations in staffing and resources currently affecting IHS limits resources for those kids most in need. Suggest coordination with the Shriver Centers for Development and Disability, and in terms of tribal communities I work with, the needs for care need to be not centralized, but mobile and able to travel to the tribal locations. Our experience working with the CDD clinicians as well as IHS clinicians has demonstrated that compliance with appts at a central site is poor, but taking the clinics to the patients achieves much better early intervention, screening, and development needs care compliance. Purchase of these kinds of mobile resources are often problematic in NIH budgets, but would encourage that the RFA include this as a possibility when its utility can be justified with respect to care.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

There is tremendous value in leveraging existing cohorts to collect standardized diverse data elements. This value is apparent from a cost-effectiveness standpoint and the utilization of proven entities with track records of effective partnerships to sustain longitudinal cohort studies. Ideal existing cohorts should be able to provide over-representation of participants from high-risk groups such as those disproportionately affected by adverse childhood outcomes and diverse racial/ethnic backgrounds. Use of existing cohorts ensures that each has the internal structures in place to successfully recruit from the existing cohort and expand upon the extant cohort through recruitment of siblings, subsequent pregnancies, etc. A combination of biomedical, psychosocial, and environmental exposure information, the availability of specimens, and consent for futures studies are all necessary in fully developing existing cohorts. A history of strong partnerships and continuity across clinics, hospitals, and community partners demonstrates the potential for long-term stability. Cohorts that are able to demonstrate the history of/ and ability to form long-term collaborations with other scientific partners and institutions, and a clear investment of one's own institution are essential for the commitment and structure needed for longitudinal studies. Cohort sites should also be able to demonstrate a large institutional commitment and investment.

Additional core elements to be considered

Additional core elements to be considered are measures of human physiology (e.g. electrocardiograph, heart rate, blood pressure, body temperature, etc.), brain activity (electroencephalography-EEG), and auditory processing (e.g. otoacoustic emissions, auditory brainstem response, etc.). Other core elements to be consider include child's behavioral development, maternal psychosocial well-being, adverse life events/adverse childhood exposures, and a broad range of exposures during pregnancy (e.g. smoking, alcohol, and other drugs).

Considerations for harmonizing data across cohorts

All proposed cohorts should have a well-developed data dictionary and derived variables listing, as well as the willingness to develop a collaborative data dictionary and derived variable set across cohorts for the current study is essential for data harmonization. Existing cohorts will already have a data coordinating center or data management structure in place. Continued involvement of the cohort's data experts will be necessary for data harmonization in the initial phase of the ECHO program. Allocation of specific budget resources toward the involvement of the original data coordination centers from existing cohorts will facilitate the transition to a consolidated, harmonized data set. In addition, designation of a specific data manager by each cohort will ensure ongoing involvement with harmonization of new and

existing data collection.

High impact areas of opportunity in addition to those listed

Other high impact areas of opportunity include the need for deliberate dissemination of research data to participating communities. This can be accomplished through descriptive aggregate data of key variables. Longitudinal studies require an extensive commitment from clinics, hospitals, schools, and tribal communities. Involving these partners directly in dissemination at regular intervals throughout the study can help maintain successful long-lasting relationships. The use of research data in high need areas presents more immediate benefits within individual communities (notably in rural and underserved communities), thus enabling community partners potential opportunities to address key health and development needs. Dissemination of findings to community health partners and key stakeholders should be expected of cohort sites (site access of data).

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

The capability of each cohort site to adapt to innovative, state-of-the-art data collection and analytic methodologies consistent with modern research advances will strengthen the overall data sample. Cohort investigators must be able to demonstrate the ability to adopt and apply new technologies for the measurement of participant data (e.g. physiology, psychosocial, and exposure related data). One option for this is the ability of cohort sites to implement ancillary studies to the primary protocol. These ancillary studies can incorporate state-of-the-art technologies that advance upon existing data while maintaining the integrity of the primary study protocol.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Safe Passage Study, a longitudinal cohort study from pregnancy through one year of infancy, of the Prenatal Alcohol in SIDS and Stillbirth (PASS) Research Network, a collaborative effort between the National Institutes of Health (NICHD, NIAAA and NIDCD); two main Clinical Site locations, one in the US Northern Plains (with sites in Sioux Falls, SD, Rapid City, SD, Pine Ridge, SD, and Spirit Lake, ND) and the other in Cape Town, South Africa; a Developmental Biology and Pathology Center; a Physiology Assessment Center; and a centralized Data Coordinating and Analysis Center (DM-Stat). The main objective of the Safe Passage Study is to investigate the relationship between prenatal alcohol exposure, stillbirth, and sudden infant death syndrome. A common protocol was developed and maintained by the PASS Steering Committee. Across locations 12,084 pregnant women were enrolled. For the purpose of the ECHO opportunity, the Northern Plains cohort will be applying independently. The Northern Plains cohort recruitment for the Safe Passage Study began in August 2007 and ended in January 2015, with a total of 5,024 women-infant pairs enrolled. Women enrolled into the cohort represent two populations prominent in the Northern Plains: white (56%) and AI/AN (42%). Pregnant women were approached to participate in the Safe Passage Study between 6 weeks gestation through delivery. The Safe Passage Study protocol is uniquely comprehensive with attention to the following: maternal demographics, medical, and obstetric history, diet, pre and postnatal psychosocial assessments (e.g., depression, anxiety), pre and postnatal exposures (e.g., alcohol, tobacco, marijuana), fetal/infant autonomic nervous system physiology, fetal growth and placental function through Doppler ultrasound, infant neurophysiology (EEG/hearing), and infant anthropometrics, medical history, facial dysmorphology, and in a large subset, assessments of infant cognitive ability and motor development were completed.

The additional IDeA States opportunity

The inclusion of the IDeA program creates opportunities that will broaden the scope of diverse partnerships within the NIH funded ECHO research program. The IDeA program will enable research that will expand services to unique populations across the United States and allows competitive opportunities for remote and rural areas. In addition, the inclusion of IDeA program states helps build infrastructures for research. Oftentimes, IDeA states have unique challenges for conducting large longitudinal studies. For example, the study catchment may cover a vast geographic area and require numerous partnerships for success. In addition, IDeA states often collaborate with other investigators at different institutions to help supplement expertise and fill gaps not available in the region. This is particularly true in IDeA states that have large rural and underserved populations. IDeA states also appreciate investment in the training of more junior investigators of diverse/under-represented groups, particularly those from AI/AN investigators.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

... I am pleased to describe the capacity within ... that could support a potential Coordinating Center for the Environmental Influences on Child Health Outcomes (ECHO) Program (The National Children's Study Alternative) in collaboration with the Dean Lynn Goldman of the GW Milken Institute School of Public Health (SPH) and Elizabeth Thom of the GW Biostatistics Center. ... is committed to optimizing the research infrastructure that supports clinical and translational research at the Children's National Health System and The George Washington University. The working "units" of the ... currently comprise an integrated network of components and programs. These resources are organized to optimize success in achieving our five strategic priorities: 1) enhancing the research infrastructure; 2) promoting investigator education, training and career development; 3) accelerating discovery across the T1 interface; 4) building community partnerships; and 5) expanding value-added partnerships. All the resources of the ... can be accessed through a system of senior staff guides and a webbased access portal ... In the revised application that the ... will submit in September 2015 for our second cycle of funding, we have significantly strengthen our ties with the SPH through the addition of seven faculty to serve as co-leads of several modules including: Collaboration and Multi-disciplinary Team Science; Community Engagement; Biostatistics, Epidemiology, and Research Design; Integrating Special Populations; Participant and Clinical Interactions; Liaison to Recruitment Innovation Centers; and Evaluation and

Continuous Improvement. Through these enhanced collaborative interactions, the ... can readily deploy our unique resources in support of a Coordinating Center proposal to provide administrative, methodological and analytical support for the ECHO Program.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

The George Washington Milken Institute School of Public Health, in partnership with the GWU Biostatistics Center, and colleagues in Psychology, the Children's National Health System, and the CTSI-CN (our CTSA-funded collaboration), is interested in the Coordinating Center (CC) function for ECHO. Based on the experience with the National Children's Study and other multi-site longitudinal studies, the ECHO/CC should be integrated to provide data management and administrative support in addition to methodological and analytical support. Members of the CC should work in partnership with the PIs and NIH study staff to create a collaborative environment for all. Core Elements: ECHO should make maximal use of data on exposures, risk factors and health outcomes. Existing studies may have collected a limited range of exposure and outcome data. ECHO should not default to the lowest common denominator due to data availability. The CC can assist in integrating data across cohorts, e.g., by developing: o Methods to impute missing data o Innovative modeling techniques o Validation studies o Relevant external databases, e.g., birth and death certificates, medical records, environmental monitoring. Focus Areas: The Focus Areas will inform the development of initial hypotheses; the CC should conduct power analyses for the four focus areas, considering requirements to assess complex genetic/environmental/behavioral interactions. These analyses can inform additional data collection efforts. The CC should use birth certificate and census data to identify significant populations that are underrepresented, in aggregate, by the existing studies. The CC should assist NIH in determining which

additional populations, if any, should be added to ECHO via additional data collection. Military-connected children and children of veterans experience unique exposures and stressors, and should be considered for inclusion. Health providers in areas with underrepresented populations (like IDeA states) can be engaged to recruit these additional subjects.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Use of existing cohorts would have a number of advantages in terms of efficient use of studies that already are underway as well as the ability to share data across study centers. Also, investigators who have successfully recruited and followed these existing cohorts potentially can provide important knowledge and expertise to ECHO. ECHO should make maximal use of this intellectual capital as well as the expertise of NIH scientists. There also are a number of potential drawbacks to the proposed plan including: (1) Existing cohorts will be comprised of different birth cohorts and there are temporal changes in a number of factors that may impact children’s health, e.g., shifts in diet, in medical care practice and coverage, in environmental exposure patterns, that will need to be addresses in the approach to leverage these existing cohorts. (2) By design the National Children’s Study was intended to be broadly representative of the entire US population. By leveraging existing cohorts, the ECHO study is likely to be unrepresentative especially since these cohorts are unlikely, themselves, to have been population based. Additional sampling may be required as noted below. (3) The ECHO study could develop standardized methodology for prospective data collection. However, it is likely to need to rely on retrospectively collected data that were not collected in a standardized fashion.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

ECHO could make maximal use of any of the data that the existing cohorts may previously have collected on exposures, risk factors and health outcomes. Prior studies may have collected a limited range of exposure and outcome data – data designed to address individual hypotheses rather than the broader set of health outcomes that may be included in ECHO. Rather than default to the lowest common ECHO can work to integrate data across cohorts, e.g., by developing:

- o Methods to impute missing data, e.g., data on individual exposures from environmental data and histories or from exposures measured later.
- o Innovative modeling techniques
- o Validation studies, e.g., studies to validate use of clinical records in lieu of direct examinations (where examinations were not conducted earlier)
- o Methods for collecting

data retrospectively (e.g., can earlier exposures be imputed from later measures?)

High impact areas of opportunity in addition to those listed

ECHO could consider a number of design features that were not included in the National Children's Study, for example:

- Extending birth cohorts by collecting data on exposures and outcomes for subsequent sibling births. Such a design can help inform genetic and environmental influences on health outcomes and is efficient in that measures of household and community exposures can apply to multiple children (albeit perhaps at very different critical exposure windows)
- Studying health outcomes, exposures, genetics and epigenetics of parents and grandparents to elucidate environmental factors that may be affecting health transgenerationally (e.g., diet, smoking)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

ECHO should anticipate advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study.

- • The price of genetic sequencing has been plummeting as high throughput platforms have become validated and more readily available. ECHO should ride this technological wave; it is not at all unreasonable to assume that similar advances will be made in epigenomics, proteomics, and metabolomics.
- • Further down the pike, and in need of a concerted development effort that should involve industry as well as the NIH and universities, is the need to develop rapid and multidimensional tools for modeling exposures ("the exposome") at multiple levels (individual and community) to increase the accuracy, availability and efficiency of measuring exposures through time. Such tools may query the environment but may also query individuals (e.g. hypothetical discoveries that may identify specific epigenetic targets for individual chemical exposures).

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The ECHO study should make maximal use of readily available and relevant external databases, e.g., birth and death certificates, birth defects registries, cancer registries, and environmental pollutant monitoring networks. In particular birth certificate data can be used to compare the demographic makeup of the existing cohorts with populations as a whole in order to understand the extent to which the studies represent the US population as a whole and potentially the need for additional data collection from subpopulations. Birth certificates in particular provide standard information on maternal age, maternal race/ethnicity, gestational age, length, weight, head circumference, address at the time of birth, and maternal smoking during pregnancy. Increasingly, electronic health records (EHR) are being employed. It is possible to combine data from multiple EHR systems; at GWU we are doing so for a large CMS study of HIV AIDs treatment in the DC Metro region. Data from maternal EHRs could help provide valid data on maternal conditions, weight gain, blood pressure, and medications during pregnancy as well as parity, prenatal health problems, and complications of labor, birth and delivery, all of which may have profound influence on children's health. Data from children's EHRs can provide important information about growth and development, and medical conditions. Where EHRs are not available ECHO could transcribe data from paper medical records. In particular, many smaller doctor's practices in the US are still in the process of transitioning to electronic medical records.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

The potential benefits of leveraging existing cohorts is that a large amount of information will have already been collected, adding to the breadth of information available. This should also streamline the process, as the time and resources to identify the populations will have been accomplished. One of the challenges will be the standardization of data elements, which will require additional efforts, given that groups will have already been collecting data may be somewhat resistant to modifying data collection from their existing protocols. Another important consideration are cultural factors (language, etc.), particularly when evaluating comparable neurobehavioral outcomes.

Additional core elements to be considered

Basic science models should be considered, as they can provide more definitive evidence of a causal relationship between environmental exposure (including all of the environmental factors listed), epigenetics, and outcome (physical, neurodevelopmental, and behavioral). The clinical data will be primarily correlative and the addition of basic science models will help to confirm the relationships, as well as evaluate the effectiveness of interventions and modifying factors. The combination of data from human populations and basic science models would be powerful.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

The Core Element of Environmental factors should include a focus on exposure to various drugs of abuse, such as alcohol, methamphetamine and cannabis. For example, it is estimated that more children suffer from fetal alcohol spectrum disorders (5% of live births, with some estimates that are even higher) than autism, and increased THC levels in available cannabis are likely to exert still to be identified effects on brain and behavioral development. Prenatal alcohol and drug exposure has many effects on physical, health, neurodevelopmental and behavioral outcome. Special efforts to obtain standardized information on these variables should be made and approaches can be obtained from current investigators and cohorts in the teratology field. Given that prenatal exposure to alcohol and other drugs of abuse is largely preventable, better elucidation of the consequences and subsequent public awareness could have a high impact on child health and outcome.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up

through childhood, available biologic or environmental specimens)
(*Submitter left answer blank*)

The additional IDeA States opportunity

(*Submitter left answer blank*)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

While the core elements include “demographics” and “environment” there is little evidence to suggest that ECHO will support analysis of how the social/cultural/economic environment influences specific aspects of child development. There are considerable disparities in the area of child health and development, and a broad view of the environments in which children grow is warranted. It is easy for “demographics” to be reduced to classifications of subjects by education, age, geography, etc. without going further to understand how the social environment supports or fails to support health. There is little debate about the importance of the family in creating and sustaining health and managing disease. Existing NIH-funded cohorts with a depth of understanding about how families are formed and function and the implications for child wellbeing include the nationally representative Panel Study of Income Dynamics Child Development Supplement as well as the Three Cities Study, National Longitudinal Study of Adolescent to Adult Health, Fragile Families and Child Wellbeing Study, and Los Angeles Family and Neighborhood Survey. ECHO should capitalize upon these existing resources, building upon them with modest investment to advance our understanding of how family dynamics influence child health and wellbeing outcomes.

Additional core elements to be considered

The social environment is a crucial factor in children’s health and development, but it is not explicitly included in the ECHO RFI. Although the core elements include “psychosocial environment,” that terminology is generally used narrowly and does not include major social environmental issues such as social structure, discrimination, family instability, intergenerational patterns of economic disadvantage, immigration, residential segregation, etc... However, recent research in many fields is beginning to show how social environment interacts with the physical environment to affect human health and child development. PAA/APC urge NIH to include population scientists who are experts in social environmental research in future ECHO planning and studies to ensure this research is addressed.

Considerations for harmonizing data across cohorts

Population scientists have extensive experience working with multiple large and complex data sets and harmonizing data for research. ECHO could greatly benefit from this expertise rather than reinventing the wheel. Population scientists also have many years of experience with issues of public use data and data confidentiality--especially given their expertise designing and maintaining large-scale, NIH-funded datasets, such as the Health and Retirement Study, Fragile Families and Child Wellbeing Study, and the Panel Study of Income Dynamics. To maximize the agency's investment and benefit to the scientific research community, ECHO data should be publicly available with proper data privacy safeguards in place. Again, population scientists have extensive expertise in this area and could be helpful during future ECHO deliberations and developments.

High impact areas of opportunity in addition to those listed

As described above, a very high impact area that is not explicitly discussed in the ECHO description is the interaction of physical and social environmental variables on health.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

The array of data collection tools, bio-measures and other strategies for gathering data are growing. ECHO could take advantage of them while also taking advantage of well established measures. The extramural research community has extensive experience in developing samples, following respondents, sharing data and protecting confidentiality. The social science community has a history of data sharing and has developed valuable approaches that bring others to the data and expand their value. ECHO has the opportunity to broaden the communities of science who are concerned about child health and who could, working together, help generate truly innovative data sets. Easily available data sets can be an especially valuable resource for junior investigators who can do robust research in the confines of funding available for them.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

If ECHO is clearly vested as an extramural project, then investigators who are responsible for existing cohorts will be motivated to participate. The NIH and especially NICHD has supported a number of such studies. AddHealth is an ongoing NICHD-funded study that has tracked individuals from adolescence through the prime childbearing ages. Understanding early risk behaviors of parents and the trajectories of their lives provides a wealth of social and behavioral data that can be augmented with data from their children. AddHealth is a large, nationally representative study that includes oversampling of racial and ethnic groups; includes siblings, and oversample of twins, and biologic as well as social measures of health. NICHD also supported the National Longitudinal Study of Youth (NLSY) cohorts including the groundbreaking inclusion of children of the respondents and direct measures of their health and development. The “children of the NLSY” demonstrated the potential to bring together different scientific communities to create a resource that many could then use. Now, with the advances in genomics the potential is only greater. The potential of a representative sample that can inform us about the health of US children is huge. This is an era of increased concern for groups that may be “left behind” and population based studies are one tool to help us understand them. To identify additional, similar cohorts, PAA and APC encourage NIH to engage the extramural community, seeking their advice and participation.

The additional IDeA States opportunity

Rather than launching new cohort or longitudinal studies in IDeA states, ECHO should consider grants to involved pediatric, environmental, and social science researchers in IDeA states in the collection and analysis of new data in extant nationally-representative longitudinal studies. ECHO is an opportunity to encourage interdisciplinary research collaboration and to advance our understanding of the complex of factors that influence children’s health. ECHO could be a landmark study, living up to the NIH history of funding groundbreaking research tools. It is important that ECHO not be diluted to achieve other goals.

Attachments: (No attachment)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

My primary recommendation is to make the Fragile Families and Child Wellbeing Study (FFCWS), an existing NICHD-funded birth cohort study (R01 HD36916, R01 HD39135, and R01 HD40421), part of the ECHO program. It is a large study of 4,898 families clustered in 20 US cities. The families (child, mother, and father) have been interviewed at birth, 1, 3, 5, 9 and 15 years old; using standardized measures/assessments on many topics, including several related to the RFI: demographics, obesity-related measures, neurodevelopment measures (mental health, ADHD, psychosocial development, cognitive ability), and many others. In addition, at age 9 and age 15 biological data was collected from the mother and child and currently a subset is being examined (R01 HD076592). Potentially more interesting is that 3 of the cities are located in states (Michigan and California) where blood spots collected at birth are stored and available for research. The Michigan site already has experience working with the Michigan Neonatal Bank in obtaining stored neonatal blood spots. Almost 200 biomarkers and compounds can be measured in dried blood spots: from genetic and epigenetic markers to environmental toxicants like lead or chemicals, to infectious agents. Combining the neonatal blood spots and other biological data already collected (DNA, methylation, bloodspots, brain imaging) would provide an outstanding resource for a wide range of research. Most importantly, the vast majority of the data are already collected and all are, or will be, publically available. This would provide the ECHO program with at least a 15-year birth cohort in a very short amount of time. In addition, FFCWS is a diverse sample that is both nationally and city-specific representative—but with an oversample of non-marital births, and the families have experienced a wide range of social and environmental exposures.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Benefits of existing cohorts include availability of samples/data and reduced lag time in terms of research output, as well as the capacity for validation of findings across distinct existing cohorts.

Drawbacks include the lack of standardization across existing cohorts.

Additional core elements to be considered

Consider engaging medical groups to leverage existing standardized data in electronic medical records - this may be particularly useful for pre-natal studies.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

Standardized assessment of immune developmental processes in parallel with microbiological and physiological maturation i.e. cross-disciplinary assessment of the same human samples

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

Home-based electronic reporting by participants, possibly incorporating existing apps, to promote data rich longitudinal data sets for analyses and cost savings.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

Sloan Foundation funded research study on the house dust fungal microbiome as it relates to the infant gut mycobiome and allergic disease development in childhood (awarded to Susan Lynch, UCSF). This study has leveraged existing house dust samples (see below) and has collected new samples (n=60 of 100 anticipated samples), the latter in conjunction with an extensive assessment of the built environment, using a questionnaire developed by building scientists at U. of Michigan. The Sloan-funded study is a sister study to a NIAID program project grant (Directed by Drs. Christine Johnson and Dennis Ownby, Henry Ford Hospital), which, amongst it's research questions, examines the relationship between the house dust bacterial microbiota in early life, the infant gut microbiome and allergic disease outcomes at age 2. Both of these studies are based on Drs. Johnson and Ownby's WHEALS birth cohort of approximately 1,000 subjects, which has amongst its repertoire of samples, paired house dust and infant stool samples collected in the first year of life, together with extensive clinical outcomes e.g. allergy, obesity etc. assessed at various time points during childhood. These children are now 10 years of age and a large majority (~95%) have been retained in the study and are currently undergoing clinical assessments. The URECA study within the Inner City Asthma Consortium possesses early life house dust samples, immunological profiles and allergic asthma outcomes for several hundred children.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Potential benefits: using existing cohorts is an efficient way for newly proposed studies. Potential drawbacks: existing data in the cohorts are likely inconsistent with each other and do not fully fit the requirement of the newly proposed studies. Thus a carefully designed research strategy that has the potential to utilize the data in different cohorts to the maximum extent and analytical strategies that are able to harmonize the data are extremely important. Existing cohorts should not be limited to those in the United States and cohorts in Europe, Asia, and Africa, etc., should also be considered.

Additional core elements to be considered

We suggest genetic influences be included in the consideration as this factor has the potential to interact with environment and also with epigenetics.

Considerations for harmonizing data across cohorts

Data harmonization across cohorts is essential in order to efficiently and effectively utilize data from different cohorts. However, each cohort has its unique features, and thus flexibility should be given to each cohort and cohort-specific data collection should be encouraged. In addition, strong expertise in data management and data mining is needed. To harmonize data across cohorts, deviation from existing approaches should be allowed. Biostatisticians/Statisticians with strong expertise are critical for data harmonization.

High impact areas of opportunity in addition to those listed

We would like to suggest to include allergies and immune responses as another two focus areas. Allergic diseases are common. About 25% of the population suffering from one or more of these conditions. Allergic mechanisms have long term effect on chronic conditions such as asthma.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

The projects will benefit from having a biostatistics core in the Coordinating Center. We suggest the biostatistics core have the following functions: 1) the ability to coordinate and communicate between different projects. This requires investigators in the biostatistics core thoroughly understand the research questions and have the desired statistic expertise in different applied areas, e.g., genetics/epigenetics. 2) the ability to design cohort-specific analytical methods to fit different features (e.g., types and measures of phenotypic and genetic/epigenetic data). It is not common that multiple cohorts will be included in projects (of one grant); however, this has the advantage that a group of investigators with diverse cohorts but similar focus area can assemble to cooperate. Although the newly collected longitudinal data will be standard cross different cohorts, the existing data can vary substantially from one cohort to another. To make valid comparisons between findings from different cohorts, specific methods are needed to process the data for each cohort, and consequently, statistic expertise with desired methodological strength, e.g., dealing with missing values or big data, is required. 3) the ability to analyze data with appropriate and advanced approaches. 4) the ability to design new

methodology that improve the efficiency and quality of data analyses for the proposed research. Expertise with track record in developing new statistical methodology is needed under this context. It is not sufficient to just administratively coordinate a project.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

Studies with peri-conceptional data but with pregnancy-related specimens are of importance. Several cohorts are within this scope including the Newborn Epigenetics Study (NEST) in Durham, the CANDLE study in Memphis, Project VIVA, Boston, and the IOW cohort in the United Kingdom. These studies have collected outcomes such as obesity, neurobehavioral, and/or respiratory. Many studies enroll participants and have a negligible proportion of minority populations. It thus will be beneficial to include cohorts that maximize the number of minorities, which will facilitate productive collaboration among investigators of diverse cohorts.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Leveraging existing cohorts is a potentially useful and cost-effective method of producing new knowledge on child health outcomes. The potential use and value depends, however, on making key decisions about the ECHO cohorts and related research initiatives based on these cohorts. First, ECHO studies must include population-based, representative cohort samples to permit the generalizability of results beyond a clinic or local geographic area. Population-based representative samples allow for the understanding of child health outcomes in a broad context that are not dependent upon the peculiarities of non-random, convenience samples. Population-based representative cohorts also allow for the explicit comparison across key population subgroups—such as race/ethnicity, gender, and socioeconomic status—so that health disparities can be addressed at the population level. Population-based representative cohort samples are furthermore critical for understanding genetic influences on child well-being because lack of population diversity in local or non-representative samples truncates environmental variation, and in turn, genetic, epigenetic, transcriptomic, and gene by environment relationships with child outcomes. Second, ECHO needs to consider an array of social science population-based cohorts in its mix. NICHD, in particular, has invested in a number of large, population-based, cohort social science studies over the past 20 years which collect data on childhood environments, family structure, health outcomes, child growth, etc. Included among these cohorts is The National Longitudinal Study of Adolescent to Adult Health (Add Health) – a longitudinal study of a nationally representative sample of adolescents (N>20,000) in grades 7-12 in the United States during the 1994-95 school year who have been followed into young adulthood with four follow-up interviews. Data collection for the fifth wave will occur in 2016-18; the cohort members will be 32-41 years old. Add Health contains unprecedented environmental, behavioral, psychosocial, biological, and genetic (including GWAS) data from early adolescence and into adulthood on a large, nationally representative

sample

Additional core elements to be considered

Clearly, the social environment – in a broad sense – needs to be a crucial element in ECHO; at present, the RFI does not indicate this. Children’s health, growth, and development depend upon a multitude of factors that fall under the umbrella of the social environment. Moreover, those social environmental factors change over time and differ across place, so understanding them is both complex and necessitates continuous monitoring and new methodologies of data collection. Social environmental factors can also interact with other determinants of child health (e.g., genetic endowment) to influence health outcomes and health behavior. Key elements of the social environment include parental characteristics, family structure and transitions, exposure to racism, processes of immigration and assimilation, residential context and mobility, school context and mobility, peer context, and more. Large social science cohort studies such as Add Health (as well as the Fragile Families Study, the Child Development Supplement of the Panel Study of Income Dynamics, and the Los Angeles Family and Neighborhood Survey) are best positioned to help the scientific community’s understanding of how the social environment influences children’s health outcomes, as well as how the social environment interacts with biological and genetic factors to influence children’s health.

Considerations for harmonizing data across cohorts

Harmonizing measures across ECHO cohorts could be both a very important and very challenging endeavor. Substantial planning and buy-in is needed. The social scientific community, particularly demographers, has a great deal of expertise in data harmonization. Consider, for example, the post-hoc harmonization of the National Health Interview Survey, called the “Integrated Health Interview Survey.” This project, conducted by the Minnesota Population Center (in collaboration with the National Center for Health Statistics), has resulted in substantial growth in the use of that nationally representative data set to US study health trends across time. Harmonizing measures across ECHO cohorts should also be inclusive of large, population-based representative samples. For example, if a harmonized measure of discrimination against African Americans is added to ECHO cohorts being followed in San Francisco, Seattle, New York, and Miami, the results of using that measure for children’s health could be very different than if it was collected and measured for the nation as a whole. That is, without measuring such concepts in large, national population-based samples, the scientific and policy communities will have no way of knowing whether such results apply to the population as a whole and/or whether key subgroups of the population experience different health impacts as a result of such an exposure.

High impact areas of opportunity in addition to those listed

As mentioned above, the social science based cohorts are very well suited to understand how the social environment interacts with genetic and epigenetic influences to influence children’s health. Moreover, the opportunity to do so using population-based data and to do so across multiple population subgroups is a very high impact area of opportunity. Second, some of the social science cohort studies, such as Add Health, provide a unique opportunity to study how detailed parental factors (e.g., biological, social, health) influence child health outcomes. Such intergenerational studies, particularly at the population level, are rare. Add Health and a couple of the other social science cohort studies provide very detailed information on parents so that child health outcomes can be studied in an intergenerational context.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

Add Health (www.cpc.unc.edu/projects/addhealth) provides a great example of how social, biological (including genetic), intergenerational, and contextual measures can be collected for a very large

nationally representative sample of Americans who are being followed across time. The data have also been publicly disseminated, with great care given to the confidentiality of respondents. The data have been very widely utilized—in the social sciences, the medical sciences, and beyond. Add Health has over 10,000 data users around the world who have produced more than 5,500 articles, books, reports, dissertations, and presentations. Over 3,000 peer-reviewed articles have been published in 350 different disciplinary journals and outlets. The innovations include the very rich social, family, peer, and school data there were collected for each adolescent; the biomarker and genetic data collected for all respondents; an embedded genetic sample of 3,000 pairs of adolescents (i.e., twins, full sibs, half-sibs, and adolescents who grew up in the same household); the linkage of birth certificate data to respondents; and health information regarding the children of the Add Health respondents after they give birth. ECHO cohorts could utilize some of the innovations and lessons from Add Health as it plans for the future.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

As mentioned above, NICHD has invested in several longstanding social science, population-based cohort studies on children and adolescents over the past two decades. Add Health is very well suited to fit into the ECHO set of studies, given its very large size, national representation, oversampling of minority groups, inclusion of social and biologic data, and its rich set of contextual (neighborhood, family, peer) measures. Although the Add Health cohort is now on average 35 years of age, it can be used in at least two ways to enhance the ECHO Program effort: 1) to collect additional information on the children of Add Health respondents (both as they are born and as they grow up)—thus, allowing for the further exploitation of the rich parental information during the preconception period, beginning in early adolescence; and 2) to provide an example of a data collection effort that is both population-based, nationally-representative, and extraordinarily rich across the social, health, and biologic domains.

The additional IDeA States opportunity

The inclusion of ongoing rich, population-based, social science cohort studies such as Add Health provide ECHO with the opportunity to gain great knowledge and expertise at a fraction of the cost it would take to start a new cohort. ECHO should seriously consider the inclusion of such cohort studies as it moves forward.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Conditions Affecting Neurocognitive Development and Learning in Early childhood (CANDLE) prenatal cohort is a unique opportunity to leverage an extant cohort to investigate the association of demographic, developmental, epigenetic, and environmental influences on asthma development. CANDLE consists of over 1400 mother-child dyads recruited during the 2nd trimester of pregnancy and is one of the largest predominately African-American (62%) extant prenatal asthma cohorts. In-person dyad visits (CV) occur at child ages of 4 weeks and at 1 (CV1), 2 (CV2), 3 (CV3), and 4.5 (CV4.5) years. CV1, CV2, and CV3 visits have been completed with completion rates of 80%, 79%, and 75%, respectively. Completion rate for age-eligible children is 82% for CV4.5. Asthma and allergic disease outcome are ascertained at ages 3 and 4.5-6 years. Continued follow-up will allow for more definitive determination of asthma outcomes and lung function assessment in older children. CANDLE is a rich resource with repeated demographic, psychosocial, and dietary (prenatal and postnatal) assessments, in addition to an extensive biological repository that includes maternal prenatal blood and urine specimens (2nd and 3rd trimesters and delivery) and cord blood and placental specimens. This wealth of data can be used to investigate the association of child asthma and lung function with numerous prenatal exposures including nutritional (antioxidant/anti-inflammatory micronutrients), psychosocial (maternal stress and related psychological correlates), and chemical exposures as well as child postnatal exposures including obesity/growth trajectory, socioemotional health, and diet. The availability of maternal specimens, cord blood, and child DNA will allow for collaborations with other cohorts to better understand contributions of genetic variants and/or epigenetic mechanisms to disease development. CANDLE includes a multidisciplinary team: PI, Frances Tyllavsky, Dr. PH. (nutrition, epidemiology), Kecia N. Carroll, M.D., M.P.H. (prenatal/early life factors and child asthma), Stephania Cormier, Ph.D. (pulmonary inflammation and immunology), Terry Hartman, Ph.D., M.P.H., R.D. (nutritional epidemiology).

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

There are several existing regional cohorts that have excellent data that can address the proposed questions. In many cases, the relevant data has been collected but the studies lack the funds to support staff and scientists to analyze questions outside of the few specific aims in original grant proposals. Putting funds into mining these incredibly rich resources is a sound investment and should be very cost-efficient and productive.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

Studies focused on rigorous characterization of the social environment are not emphasized as they should be in this call. This critical aspect of developmental science should be included within the emphases.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

Few longitudinal cohorts in the United States assess how environmental influences (i.e. physical, chemical, biological, and psychosocial) affect child health in the urban south, where some of the largest disparities in obesity, diabetes, asthma, and cognitive and behavioral outcomes are observed. In part, this reflects the challenges of recruiting and maintaining a cohort of socioeconomically and racially diverse pregnant women and their children in this part of the country. We suggest that the NIH ECHO committee consider the Conditions Affecting Neurocognitive Development and Learning in Early Life (CANDLE) study to address this important gap in U.S. child health research. In 2006, we enrolled a sample of 1503 pregnant women from Shelby County, Tennessee who reflect the county's demographics: primarily African American (68%) and Caucasian (32%) with notable socioeconomic diversity at the individual and neighborhood level. Mothers and their children have participated in clinic, home and phone assessments from throughout pregnancy and then annually through age 4 of the child, with strong retention rates. Assessments include objective and subjective measures of: maternal psychosocial and nutritional environment; labor and delivery outcomes; parenting and family structure; and child neurocognitive, nutritional, psychosocial and physical health assessments. Stored biological samples include maternal blood and urine during pregnancy; offspring cord blood and placental tissue; maternal, paternal and offspring buccal cells; and child blood and hair (see <http://candlestudy.com/research/guidelines-collaboration> for details). In combination with the rich existing psychosocial and physical health data, these biological samples offer the opportunity to examine CANDLE children's chemical and non-chemical exposures across development. The cohort is also linked to several administrative databases with additional environmental toxin exposures (e.g. air quality, crime, concentrated poverty) and national Child Opportunity Index ratings. We believe this cohort provides a unique opportunity to rigorously examine environmental influences on child health

outcomes in an understudied region of the U.S.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

Predictive modeling has been a key to understanding and evaluation of knowledge. It validates the knowledge about risk factors for various conditions in the context of real life. Predictive modeling can serve as a framework to obtain the best guidelines for future actions by combining knowledge from multiple levels of hierarchy (biomarkers, tissue, organ, person, social networks, family history, community characteristics, environment, and policy). In order to incorporate the wealth of such information a number of approaches have recently emerged. One set of approaches deals with Data Science and the ways large (and small) amounts of diverse data can be connected and “harmonized”. Another approach is Systems Science, which combines statistical and mechanistic models to incorporate feedback loops and nonlinearities in biological/physiological processes. Finally, over the last several years, within-subject data analysis and modeling have become extremely relevant. With recent advances in electronic medical records and biological and physiological sensors, it is now possible to monitor and analyze health and risk factors in real time. Although the collection of large amounts of “intensive” data poses new challenges in the design, quality, and ownership of the data, one thing is evident: data collected by an individual and for the use by that individual can have a strong impact on that individual’s health. Within-subject analysis is critical to the improvement of health because it can dramatically reduce uncertainty associated with more traditional population-based clinical research. RTI is well positioned to construct predictive models and has been awarded grants from NIDA and NIAAA to

develop methodology aimed at understanding which treatment works for whom and why. Collaborative work with biological and digital sensor laboratories allows us to develop new technologies for real time measurement and prediction of critical health outcomes.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

A factor of concern in the National Children’s Study was the cost and complexity of data capture, aggregation, and normalization. Future efforts like ECHO may benefit by leveraging the reuse of data that already exists or can easily be collected. One ready source of data is electronic health records (EHRs). Adoption of EHRs has accelerated over the past decade and now exceeds 75 percent in both acute and ambulatory settings, creating a vast body of clinical data available for clinical research. Many barriers to the use of EHRs remain. For instance, data may be missing in current EHRs, data is often not in discrete or standard form or is contained in free text notes, making extraction difficult, and most EHRs do not yet offer standard application programming interfaces for research queries. However, the accessibility and quality of data contained in EHRs is rapidly improving, and they should become a useful source of rich clinical data within several years. There are others resources that should also be considered for use in ECHO. Patient portals are in widespread use and are often directly connected to EHRs. They provide a mechanism for direct collection of data from patients. Smartphones are another mechanism for direct data capture. They are ubiquitous, and smartphone applications make it easy to capture and manipulate data prior to aggregation for use in studies. Finally “the internet of things” is rapidly changing the way data is collected, adding the possibility of direct collection of data from a variety of devices either worn by research subjects or present in their homes. My organization has expertise in the evaluation and use of these new data collection methods and highly recommend they be utilized by ECHO.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major

health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

The PhenX Toolkit, www.phenxtoolkit.org is funded as a Genomic Resource by NHGRI and co-funded by NIDA. The Toolkit provides standard measures and detailed protocols for collecting human phenotypes and environmental exposures. The Toolkit includes search and browse features to help investigators find measures of interest and tools to help integrate them into their study design. The PhenX Toolkit is Web-based and is publicly available for use, at no cost. PhenX measures are selected by working groups of experts and address many of the Core Elements mentioned in the RFI (demographics, nutrition, physical activity, psychosocial and social environment, respiratory, obesity and mental health). To ensure that ECHO study data is comparable, it will be important to require the use of standard data collection methods for the Core Elements and Focus Area, whenever possible. In several cases, NIH Institutes have supported addition of measures to the Toolkit in order to better coordinate the research of their grantees (e.g. Substance Abuse and Addiction and Mental Health research), something similar could be done to support this effort. It will also be important to be able to harmonize data collected via standard methods/protocols with legacy data from extant cohorts. With respect to legacy data associated with existing cohorts, PhenX has experience “mapping” PhenX variables to a variety of study variables, including study variables in the database of Genotypes and Phenotypes (dbGaP). Mapping PhenX measures to legacy metadata makes it easier for investigators to identify and leverage relevant legacy data. In collaboration with REDCap, <http://project-redcap.org>, PhenX protocols are being provided as zip instrument files that can be directly uploaded to a REDCap study design, which is also available as a mobile application. Use of PhenX measures will promote data sharing among ECHO investigators, with the broader research community and extant cohorts.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

Response to Core Elements is also applicable here.

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

Attachments: *(No attachment)*

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

A major benefit of leveraging existing cohorts of children whose mothers were recruited pregnancy is the availability of prenatal exposure data. The in-utero environment has been shown to be one of the most critical determinants of child and adulthood development and health.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Eunice Kennedy Shriver NICHD MFMU Network is a well established group of clinical centers and a coordinating center conducting trials and observational studies in pregnant women. Prenatal and pregnancy outcome data are collected with consistent definitions across studies by trained research personnel, resulting in very well characterized and consistently defined prenatal exposures. For all of the studies, women are asked for permission to contact them for future research. The Network has considerable experience in conducting follow-up studies on the children from the studies, both pre-planned and those not initiated until after the completion of the main study. Follow-up rates have been excellent (for example 93% at 5 years for one study), although the population is diverse with

approximately one-third Hispanic and one-third African American depending on the study. There are several cohorts that may be of interest, including the following. The Network recently completed a randomized trial of 2831 women randomized between who were at risk for late preterm delivery (from 34 to 36 weeks) to assess whether antenatal corticosteroids improves short-term respiratory morbidity in their offspring. Studies of children born in the late preterm period suggest an increased risk of asthma and pulmonary dysfunction and poorer neurodevelopment than those born at term. However, these studies are not definitive and there is a substantial gap in knowledge about longer-term consequences of late preterm birth. The MFMU Network is planning a follow-up study to rigorously evaluate asthma and other long term respiratory outcomes, as well as neurocognitive outcomes, including IQ (WISC-IV), behavior (Child Behavior Checklist) and autism (Social Responsiveness Scale). For a subset of the patients, we have maternal and infant DNA samples; it is planned to collect samples on the remaining mother-child dyads.

The additional IDeA States opportunity

(Submitter left answer blank)

Attachments: *(No attachment)*

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

[Respondent] supports the general approach of seeking to leverage existing cohorts and related resources to the greatest extent possible to expedite research, avoid duplicative activities and, ultimately, to use scarce public monies as wisely and efficiently as possible. At the same time, we would caution that NIH must set a high bar as to the strength and quality of such cohorts to ensure those used in this project are sufficient for the research needs at hand. We urge NIH to not adopt a blanket prohibition on developing new cohorts, as such a position may negatively impact the pursuit of meritorious projects where high-quality extant cohorts simply do not exist. We would also encourage the NIH to consider possible ways to add components or modules to existing studies without jeopardizing the quality of the data gathered. [Respondent] supports the premise of collecting standardized data and asking standardized questions to conduct the “apples to apples” comparison needed to provide maximum impact. At the same time, we would urge NIH to recognize the ever-changing nature of science and the need to ask new questions and retire others and to include flexibility to permit such amendments as necessary. For example, the previous longitudinal studies of the benefit of specific mental health interventions for abused and neglected children did not collect information needed to understand if the services being provided specifically addressed trauma treatment or were evidence-based. Most of these studies began before either “evidence-based” treatments or “trauma-informed” practice became part of the current landscape of intervention for families. As a result, new outcome studies are needed that collect mental health treatment data in a more nuanced way than was possible in the 1990’s.

Additional core elements to be considered

[Respondent] is pleased that NIH is defining “environmental exposures” in a broad sense and is explicit in including psychosocial factors in the study plan. It’s critical that the social environment be examined along with the physical. Psychosocial factors must include exposure to Adverse Childhood Experiences

(ACEs) such as child abuse and neglect (CAN), as the developmental effect of these experiences is profound and must be appropriately studied as part of this initiative. Based on reported incidents, about 700,000 children are abused each year and that 40% do not receive treatment. We're also seeing a burgeoning body of evidence indicating that children who are abused are at much greater risk of developing several leading causes of death later in life including, Alzheimer's disease, heart disease, cancer, hepatitis and depression. Studies show that repeated exposure to ACEs affects a variety of biological systems including the nervous, endocrine and circulatory system and immunity and inflammatory responses. Additionally, the Long-Term Consequences of CAN on Adult Economic Well-Being study demonstrated abused and neglected children experience enduring economic consequences. CDC estimated the lifetime costs for a single year's cohort of abused or neglected children will be over \$124 Billion. Simply put, we know CAN and other ACEs often result in life-long adverse health outcomes and must ensure that this study addresses this crisis appropriately. [Respondent] recommends that ACEs be established as an explicit focus area. In doing so, NIH will send a signal as to the importance of this field and the need for further inquiry and will produce a framework to advance our understanding of this topic over years to come. The LONGSCAN and NSCAW studies would be logical recipients for explicit funding for participant follow-on data regarding adult behavior and health as well as adding explicit genomic and proteomic data collection.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

[Respondent] wishes to amplify our above comment regarding our recommendation to develop an additional focus area on ACEs in the proposal. We believe a focus on ACEs would be broad enough to encompass multiple conditions and biological systems, yet focused enough to enable concentrated attention on this important issue. In including this focus, we should focus on the impact of ACEs throughout the various stages of development ranging from pre-conception and in-utero to post-natal, infancy, childhood, adolescence and young adulthood. The body of evidence available today suggests that the severity of ACEs changes depending on the adverse event and the child's age. For example, while emotional and physical abuse may have the most deleterious impact among adverse experiences in middle childhood and sexual abuse for adolescents, young childhood observations of parental intimate partner maltreatment appear to explain more variance in depression and conduct disorder. We are fortunate to have a foundational body of evidence via the CDC's ACEs study upon which we can build a further research platform. As a result of the CDC's work, we know that about two-thirds of the 17,000 study participants were exposed to at least one ACE and that more than one in five reported incurring three or more ACEs. As respondent's ACE score increased, meaning they were exposed to a larger number of events, so did their risk of developing multiple serious health conditions and, ultimately, an early death. However, this work may not be sufficiently nuanced. As noted earlier, it's likely that all ACEs do not have equal impact at all ages. Further, the retrospective studies of ACEs miss important differences in the number of adverse experiences as the categorical indication of having experienced a specific adverse experience and may not address the total number of specific events, nor the duration of that experience.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

We know of two major studies that have longitudinal data on child experiences and function, with family and community data that would help determine the genetic and proteomic linkages of adverse childhood experiences and adult outcomes. The first would be a large undertaking that would use data from over 6,000 children in the child welfare system that were enrolled in the following three year prospective study. This study, the National Survey of Child and Adolescent Well-being (NSCAW) study, collected extensive data about the child, the family environment, and interventions. Six to 10 years has passed since this study was completed and most of the participants are now young adults spread across the country. Additional resources could locate these participants and examine their function as well as their genomics and proteomics and contribute to our understanding of how adverse childhood experiences are related to cancer, heart disease, GI disease, and inflammatory conditions. A second and potentially easier longitudinal add-on would be to the LONGSCAN study. This study was initiated in 1990 and followed 1,354 children who were under the age of 4 at recruitment. It collected a myriad of data as the children were seen at 2 year intervals, and at ages 12, 14, 16, and 18 were asked to report on their own maltreatment experiences. Social service records were also examined for each participant child for official reports of maltreatment. These participants are also now adults. A recent NIDA-funded follow on study on LONGSCAN followed approximately 40% of the sample. Resources to make possible the tracking of the entire sample and the addition of biological measures would greatly enhance our understanding of the link between adverse experiences and adult disease.

The additional IDeA States opportunity

(Submitter left answer blank)

Attachments: *(No attachment)*

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

[Respondent] appreciates the intent to leverage existing cohorts to advance the refocused NCS initiative. At the same time, we are concerned that existing cohorts may be insufficient to answer the questions posed by the revised study and would caution NIH to avoid investing sizeable amounts of resource if such cohorts are inadequate. To address this concern, we encourage NIH to develop a mechanism to evaluate and certify the quality of such cohorts for use in the project to ensure that any used are of the appropriate quality, depth, size and other attributes necessary for the research task at hand. We also support the idea of NIH publishing and maintaining a listing of such cohorts, which would help the pediatric and greater research communities know what is available today and where gaps or deficiencies may lie. Beyond this point, [Respondent] believes strongly that basic science must be integrated within this proposal for it to succeed. Multiple stakeholders, including Congress, have expressed similar concerns and we urge the NIH to address these in the RFAs. We have many gaps and needs in the pediatric space that need to be addressed. The sizeable resources being made available for the NCS follow-on should be deployed to address these concerns, including by supporting the

acquisition of much-needed shared core research infrastructure and in supporting the training of early career investigators interested in pursuing a career in pediatrics.

Additional core elements to be considered

As noted above, [Respondent] believes strongly that any effort to re-envision the NCS must include the integration of basic science, an element that was lacking during the first round of the NCS. Absent such an integration, it is our belief that the revised study will fail to achieve its potential. Congress has recognized this point with both the House and Senate Committees on Appropriations including language in their respective Fiscal Year 2016 Labor, HHS and Education appropriations acts making this point. Additionally, Congress has within the past 2 years enacted legislation (PL 113-55) authorizing the establishment of the National Pediatric Research Network, which focuses heavily on supporting basic pediatric research. Furthermore, [Respondent] believes that the support for basic research much include direct support for basic research infrastructure in the form of shared core technologies that can be used by multiple institutions to generate hypotheses and to discharge research to make good use of the data collected by the project. Collecting data is an important but small step in the larger children's health research arena. If we hope to make a difference in the health and well-being of our children, we must ensure this project directly supports the discharge of basic research.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

As the nation's leading children's hospital, [Respondent] regularly serves patients from all 50 states and beyond. This service includes both clinical care and research initiatives, including clinical trials. We understand well the challenges when it comes to recruiting pediatric patients from rural and other underserved locations and appreciate NIH's interest in addressing this problem through the IDeA component of the project, and we note that four of the six states in our primary service area of New England are IDeA states. At the same time, we have some concerns to air. First off, we are concerned that while meritorious, this project does not fit within the broader focus of the proposed NCS revamp. It is the only clinical/translational element stipulated in the RFI and a strong link or connection to the overall project has not yet been made, in our view. We would urge NIH to paint a clearer picture of the desired goals and outcomes of this project so that the research community can better understand and evaluate it. On the proposal itself, we are concerned that the wording in the RFI suggests potential

limitations to initiatives operating in IDeA states only. Such a policy, however, would preclude participation of many of the nation's leading pediatric clinical trials sites. We urge NIH not to include such a prohibition on applications. Instead of limiting institutions, the project should instead encourage and provide a preference to applicants with significant engagement of IDeA state centers. By including such a focus and related language, NIH can achieve the goals of training clinical trialists in IDeA states to support recruitment and enrollment efforts and ensure that the most qualified institutions are able to compete for this training work.

Attachments: (*No attachment*)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

[1] Collect maternal and paternal phenotype and exposome information such as age, body mass index and smoking status at the time of conception and/or during gestation as certain parental attributes have been associated with subsequent developmental and health outcomes of the child through epigenetic mechanisms, akin to a generalized parent-of-origin effect. [2] Environmental factors should include socio-economic conditions. [3] Telomere variations have been associated with different environmental exposures and chronic notably age-related disorders. Longitudinal variation of telomeres in different cell types during childhood and how they are modulated by the exposome is not completely understood. This pattern of variation could be a way to uncover critical periods in early human growth that are associated with age-related disorders, akin to nephron number at birth predetermining hypertension.

Additional core elements to be considered

(*Submitter left answer blank*)

Considerations for harmonizing data across cohorts

Modeling and minimizing technical batch effects at locational, temporal and operational levels: With regards to omics data associated with each study subject such as transcriptomic or epigenetic profiles, each omics data modality will likely be generated by a distinct study center at different time points during the study duration given the vast scale of this study. This could lead to widely known batch effects at both locational, temporal and operational levels in resulting data that will compromise the aim of harnessing different synergies inherent in the study's overall design by integrating and synthesizing multi-factorial data. All participating study centers should have in place a common set of standard operating procedures and "best practices" for omic data generation prior to conducting such experiments in order to account for and minimize potential batch effects. For example, one could establish a reference or standardized sample cohort that will be measured by every study center in every omics data generation experiment instance, and there be dynamic real-time coordination of the order and design of sample experiments conducted across all study centers.

High impact areas of opportunity in addition to those listed

(*Submitter left answer blank*)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(*Submitter left answer blank*)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements The key benefit is the larger sample which enable not only multiple exposure variables (e.g., chemical or nutritional mixtures/combinations, epigenomic and genomic regions) to be evaluated in relation to common outcomes including early signs of obesity, neurodevelopmental outcomes, cardiometabolic risk and even malignancies, while adjusting for covariates. The drawbacks are that scientists are interested in specific exposures and/or outcomes, for which extensive questionnaire data if often collected, while areas of less interest are given cursory attention. Combining/harmonizing data from these multiple data sets from different scientists could be challenging. This is why there is a need to have core elements that are standardized across questionnaires. One example for instance is the questionnaire of the International Study on Asthma and Allergy in Children (ISAAC) questionnaire, which was used in more than 100 studies.

Additional core elements to be considered

Additional core elements to be considered I advocate for including nutrition and physical activity data at basic level affordable level where all groups collect the same data. This could be the Block or other adaptation of the dietary questionnaire or 24 hour dietary recall with comparable intervals between assessments, preferable at the same ages. These will be key not only because their assessment varies widely across studies, but also as we look forward to interventions, this information including doses will be critical. In addition, I would advocate deliberate inclusion of minorities, even though we know it may cost more. We suggest that pregnancy conditions and environmental exposures during the prenatal period are critical to child health outcomes and as such should be an explicit Core Element. Particularly, information about pregnancy conditions will allow the identification of ways to interrupt the transmission of parental risks to the next generation. The interaction of genetic, environmental, epigenetic data, and gene expression during pregnancy and in neonates can be used to identify children who are at a higher risk and allocate them to proven success treatment regimes (precision medicine applied in a public health setting). In order to use of results of cohort studies to improve public health, we believe that it is essential, to include small projects (R21) or appropriate funding mechanisms, with a short turn around period, that allow the investigators to quickly respond to novel findings and test their proof-of-concept.

Considerations for harmonizing data across cohorts

Considerations for harmonizing data across cohorts This is a critical piece as participating scientists will have to agree on key elements that can be easily harmonized. Conversely, it will be important to provide flexibility so as to not stifle creativity, and with it limit potential for new discoveries. Core data that allow for harmonization should be no more than 50% of the questionnaire. Our experience has shown that collaboration with other cohort studies provide the necessary opportunity to replicate findings of a single cohort in other groups. However, we also need to adapt the review system to accommodate such 'non-innovative' approaches.

High impact areas of opportunity in addition to those listed

High impact areas of opportunity in addition to those listed As large cohort studies among adults (e.g. the Nurses and Health Professionals Studies) have shown in the last two decades, there are core risk factors that influence the top chronic diseases that are in the top five causes of mortality in the US and elsewhere. They include cardiovascular diseases, diabetes and cancer. Therefore, for high impact, inquiry (questionnaires) should ensure collection of these key risk factors in early life. This will enable data capture of these exposures at an earlier age and facilitate some comparisons with data in adulthood. In addition, immune processes are closely related to all focus areas (respiratory health, obesity, neonatal outcomes, and neurodevelopment). Thus we suggest the explicit inclusion of immune processes as an additional focus area. Immune processes and related epigenetic effects are relatively easy to determine during pregnancy and in cord blood and will aid the development of better prediction models.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

Every researcher has experienced the frustration that comes with the inability to adapt data and specimen collection as additional data become available. We certainly experienced in in the NEST cohort. I advocate for a separate budget that should be requested for only when adapting existing studies to state of the art data and specimen collection. Such a budget should not be subject to standard grant deadlines and should be reviewable by the Program Official and considered for additional funding.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

We propose to evaluate obesity and early cardiometabolic risk markers in children and follow children from periconception to puberty. These data could be merged with existing cohort data. It will be important to identify and group studies as follows, at a minimum to ensure we cover the lifespan. 1. Studies with periconceptual data (some collected retrospectively) but with pregnancy-related specimens such as whole blood collected in the first 16 weeks of pregnancy (the life span of erythrocytes) in order to include, at least some exposures e.g. folate or metals such as lead that attach to erythrocytes. There are several cohorts that can be tapped including the Newborn Epigenetics Study (NEST) in Durham, CANDLE, Project VIVA and the IOW cohort. The NEST program has over 2000 mother infant pairs who meet these criteria. These studies also have collected at least three outcomes (obesity, neurobehavioral and respiratory). 2. Many studies enroll participants and have a negligible proportion of minority populations who also tend to not only have a higher prevalence of exposures such as heavy metals, poorer nutrition, stress etc, but also have a higher risk for outcomes such as obesity, respiratory diseases and neurobehavioral outcomes such as ADHD. It will therefore be critical to include cohorts

that maximize the number of minorities. • Newborn Epigenetic Birth Cohort Study (NEST) and child follow-up studies. 1R01DK085173, 1R01ES016772, 1R01HD084487, 5P01ES022831 o N ~ 2000 women from community cohort enrolled close to their first trimester. ? Cohort features: prenatal blood samples, cord blood, ongoing collection of child saliva and blood; epigenetic data, electronic health records data, measured weight for infants and children, and ongoing data being collected on neurodevelopment.

The additional IDeA States opportunity

I think there should be a two pronged strategy. The first is to use existing cohorts to gain as much information as possible. A second strategy is to encourage the development of new cohorts--our group recently submitted such a proposal to focus more closely on gestation and the first two years of life. Both strategies will require collaborative efforts which facilitate merging data sets. But they also provide autonomy which will facilitate breaking new ground.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Violence and injuries are important contributors to child health, but there is much we don't know. • Core elements: Consider the built environment vis-à-vis the risk of injury. Injuries to young and school age children occur mainly in the home or immediate neighborhood. The risk of injuries is clearly related to the built environment in terms of quality of the housing stock, volume of traffic in roads in the neighborhood, exercise amenities such as parks and playgrounds, zoning of the neighborhood, transportation patterns. In addition, when considering childhood outcomes, the structure of the neighborhood has a major influence on developmental outcomes and the risk of delinquency and violence. Measuring factors such as neighborhood cohesion, physical disorder, physical decay, street safety, residential mobility and concentrated disadvantage. Child abuse affects 10-15% of children. Measurement of the degree of child maltreatment will have an important influence on child outcomes.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

• Outcomes: Injuries and risk of injuries are very tied to a number of these outcomes including obesity, childhood outcomes, and neurodevelopment. Traumatic brain injury is the most common cause of acquired impaired neurodevelopment. Obesity is clearly related to physical activity, but the level of physical activity is affected by environmental factors in the community including perceptions of safety and safety oriented design. There is evidence that children's exposure to violence can result in changes in DNA, and increases the risk of obesity and chronic disease, although the exact mechanism of these changes is not known. Exposure to violence increases a woman's risk of certain chronic diseases, and 1 in 4 women have experienced intimate partner violence in their lifetimes. We do not know how maternal exposure to violence affects fetal development and child outcomes. The combined effects of physical injury and environmental factors, particularly those that may impact social, cognitive or physical development is unknown.

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Violence and injuries remain the leading causes of death for children. Many environmental factors -- physical, chemical, biological, psychosocial, natural and built environments -- contribute heavily to violence and injuries in children. However, there is much that we don't know.

Additional core elements to be considered

Closely consider the built, physical and natural environments with respect to the risk of violence and injury. The risk of violence and injuries has been related to the built environment from an emerging, robust, evidence-base of scientific studies in terms of blighted urban environments (land and buildings), proximity of natural spaces, quality of the housing stock, volume and speed of traffic in roads in the neighborhood, exercise amenities such as parks and playgrounds, zoning of the neighborhood, and transportation patterns. Neighborhood structure can have major influences on developmental outcomes and the risk of delinquency and violence. Measuring factors such as urban blight, neighborhood cohesion, physical disorder, physical decay, street safety, residential mobility and concentrated disadvantage could be very important and their long term impact on child violence, maltreatment, and injuries would be very important.

Considerations for harmonizing data across cohorts

As with syndemics, injuries and risk of injuries are very tied to a number of outcomes including obesity, childhood outcomes, and neurodevelopment. Traumatic brain injury is the most common cause of acquired impaired neurodevelopment. Obesity is clearly related to physical activity, but the level of physical activity is affected by environmental factors in the community including perceptions of safety and safety oriented design. There is evidence that children's exposure to violence can result in changes in DNA, and increases the risk of obesity and chronic disease, although the exact mechanism of these changes is not known. Exposure to violence increases a woman's risk of certain chronic diseases, and 1 in 4 women have experienced intimate partner violence in their lifetimes. We do not know how

maternal exposure to violence affects fetal development and child outcomes. The combined effects of physical injury and environmental factors, particularly those that may impact social, cognitive or physical development is unknown.

High impact areas of opportunity in addition to those listed

As with syndemics, injuries and risk of injuries are very tied to a number of outcomes including obesity, childhood outcomes, and neurodevelopment. Traumatic brain injury is the most common cause of acquired impaired neurodevelopment. Obesity is clearly related to physical activity, but the level of physical activity is affected by environmental factors in the community including perceptions of safety and safety oriented design. There is evidence that children's exposure to violence can result in changes in DNA, and increases the risk of obesity and chronic disease, although the exact mechanism of these changes is not known. Exposure to violence increases a woman's risk of certain chronic diseases, and 1 in 4 women have experienced intimate partner violence in their lifetimes. We do not know how maternal exposure to violence affects fetal development and child outcomes. The combined effects of physical injury and environmental factors, particularly those that may impact social, cognitive or physical development is unknown.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Leveraging existing studies to collect standard data elements maximizes the benefits of cohort studies while minimizing cost. Pooled results can increase the generalizability of results, help uncover effects of interest that are small but important, and increase the number of observations of infrequent results. In addition, a through a review of existing pediatric longitudinal research cohorts can identify important gaps in existing research (such as the health considerations of rural children mentioned in the RFI). Combining data across studies, however, is rarely as easy or as simple as appending data files together. It will be important that the Data Coordinating Center take an active role in learning the nuances of how Core Elements are collected in each study, including details such as how the data is collected (CAPI, CATI, internet based) along with the accompanying study choreography. Such inconsistencies across cohorts have been shown to impact participant responses. When exploring the best way to standardize research measures across existing cohorts, the Data Coordinating Center may consider first running a

small scale pilot study to test their procedures.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

In order to create high quality harmonized datasets, it will be crucial to have one central experienced Data Coordinating Center that can work collaboratively with scientists across the various extant cohorts. Lessons learned from the National Children's Study (NCS) indicate that one central data repository receiving data that has been integrated across Information Management System (IMS) platforms would be the most streamlined, efficient, and cost effective way to ensure proper data harmonization across longitudinal studies. As a first step in prospective harmonization, the Data Coordinating Center can develop a list of the core ECHO data elements and desired code list for each element, along with details on how this target data is currently being collected across cohorts. In many cases, previously collected data may be able to be preserved through re-mapping and/or collapsing values. A well thought out, phased-in roll out plan will minimize the need for future changes and will ensure new data collections and procedures are implemented simultaneously. A central data repository will allow real-time rigorous quality assurance and quality control to ensure the accuracy and completeness of harmonization. In addition, results can quickly and easily be disseminated to stakeholders, shortening the time between data collection and release of scientific findings to the pediatric community. The use of ontologies also facilitate data harmonization. Consistent use of shared ontologies will increase the utility of ECHO data collected by numerous studies.

High impact areas of opportunity in addition to those listed

ECHO can leverage the NCS Archive infrastructure currently being developed, which will be completed by the launch of ECHO, for collecting and sharing data and samples, to centralize research results, and securely collaborate. The Archive will include protocol, variable, and instrument search tools to help researchers understand the NCS data. The same tools could be implemented real-time to help coordinate and synchronize the operations of the different cohort location. The processes developed to document, track, and share data and samples from the Archive to researchers could be reversed to track data and samples coming to a centralized location from dispersed cohort teams. The information coming in could then be turned back for general use within the existing processes. The Archive will be establishing secure virtual environments for data analysis of existing NCS PII/PHI data. These same secure environments could be used by ECHO partners to collaborate on research projects, papers, and other academic endeavors. Having a centralizing research environment can standardize available resources and minimize security risks. A high impact tool that could transfer from the NCS is a single, centralized application for instrument development and distribution. The NCS tool, Vanguard Instrument Central, facilitated development and entry of instrument into a system a single time, from which definable electronic versions could be generated (i.e. OMB, annotate, or PAPI). The tool was developed to export files for the three NCS data collection platforms to eliminate the duplicative and error susceptible effort of re-keying an instrument by platform. A similar tool could benefit the ECHO design serving as a single point for ECHO questionnaires and as a central repository for all questions to facilitate sharing amongst cohorts. A centralized tool would reduce the burden on individual cohort teams once a link between the tool and the data collection platform is built.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

When analyzing data collected across different studies, it is important to adjust for the strengths and

possible weaknesses of extant cohort. Available statistical tools for judging the relative strength of any specific dataset, data source, or approaches for combing data across sources include Bayesian pooling approaches for combining data relative to inherent variability in the data, post-stratification approaches for dealing with possible sampling bias, and metadata statistical techniques for creating weights reflecting the relative usefulness of data from competing sources. Included in the repository can be simple descriptive statistics to help guide users. Also, software can be developed that allow users to pool information across repositories in an informative fashion. Modern data repositories are a mix of efficient warehousing techniques combined with tools that guide the user's choice of data set and provide information about data usefulness. Implementation of data retention design should, at a minimum, include framework for storing and sharing data in a non-proprietary, machine readable format. Specification, such as the Resource Description Framework (RDF) and OWL Web Ontology Language, can be used to tie in metadata and datasets and allow defining relationships between similar concepts. Machine readable frameworks would allow greater power in searching and browsing of data and could positively affect detectability of desired search.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)
(*Submitter left answer blank*)

The additional IDeA States opportunity

(*Submitter left answer blank*)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

While using extant cohorts can be efficient, there is concern about whether the quantity, quality, diversity, and inclusion within existing available cohorts is sufficient to answer the important research questions. There is a need to inventory existing cohorts to assess the adequacy of this approach. If the National Institutes of Health (NIH) determines it to be expedient to focus initially on supporting extant cohorts, we urge the NIH to use its analysis of these existing cohorts to devise a strategy for addressing identified gaps, which may include the creation of new cohorts. In considering potential cohorts, it would be important to include those that span the early life course from preconception, prenatal, childhood, adolescence, through young adulthood. While existing cohorts may include children, preconception and prenatal antecedents to later disease are extremely important. Similarly, the ability to follow children through childhood, adolescence, and early adulthood would be essential.

Translational science will benefit greatly from a life-course approach that focuses on the developmental origins of health and disease and prevention of disease across generations, especially with conditions such as obesity. Existing cohorts that have existing data on socio-environmental factors and have already collected biological samples should be prioritized to increase study efficiency and enhance study across the life course, especially given the need for additional focus on health disparities (see next section). Adding a cohort study to other large surveys (e.g. Pregnancy Risk Assessment Monitoring System [PRAMS], National Health and Nutrition Examination Survey [NHANES]) may also be a strategy

that can utilize previously collected data.

Additional core elements to be considered

As an original focus in the Children Health Act of 2000, health disparities needs to continue to be prioritized in the core elements and selection of ECHO studies. ECHO studies must ensure a diverse population of children in race/ethnicity, language preference and English proficiency, socioeconomic status, immigrant status and acculturation. Consideration should also be given to additional measures of health literacy and discrimination which further address mechanisms for differential health outcomes. There is substantially greater racial/ethnic diversity among children than the population as a whole. The 2010 Census revealed the population of Latino and Asian children grew by 5.5 million, while the population of white children declined by 4.3 million from 2000-2010. It is projected that minority children will outnumber Caucasian children by 2020. A large portion of the increasing diversity also is driven by the substantial growth in immigrant families over the last several years; nearly a quarter of children in the United States have an immigrant parent. Healthcare disparities and families with limited English proficiency are particularly salient issues in pediatrics. To address the roots of child health problems and inequities, greater attention needs to be paid to the social determinants of health. Socio-environmental factors are extremely important to include. Family and neighborhood context must be measured, including family health, neighborhood collective efficacy, community violence, and community assets. Extant cohorts that have been particularly successful in recruiting vulnerable populations should be prioritized.

Considerations for harmonizing data across cohorts

We are supportive of harmonizing data across cohorts.

High impact areas of opportunity in addition to those listed

We encourage the NIH to consider the many existing pediatric clinical research networks in designing a National Children's Study alternative and to support research on the full range of clinical conditions that children face. In order to study relatively rare conditions, as often occurs in pediatrics, these networks provide the multi-site platform that is needed to develop studies with adequate sample size. Over the last several years, the [Respondent] has worked to develop a coalition of these pediatric research networks, a number of which have the capacity to follow children from very young ages through adolescence and young adulthood. Some also have addressed/included community and social variables in their data. [Respondent] has identified over 80 clinical research networks, covering primary and specialty care, and we have also successfully run a nation-wide primary care practice based research network for over 25 years. [Respondent] would be happy to share with the NIH its knowledge and experience in this area. For example, Practice-Based Research Networks (PBRNs) bring together primary care practices, health services researchers, systems administrators, and the community to answer the needs of patients across the age spectrum. PBRNs have the capability to follow cohorts over time, and some can meet the expectations we lay out in our response to 1a. The PBRN model of embedding research into practice and communities, places PBRNs at the forefront of improving the health and wellbeing of children and adolescents and should be considered for ECHO studies. An example of a successful PBRN is the AAP's Pediatric Research in Office Settings (PROS) program.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

Extant cohorts that connect to and utilize data from electronic medical records and other sources of existing data (e.g. birth records, school data) should be prioritized. Collection of neighborhood and environmental exposure data should use state-of-the-art methods.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

We support the four proposed focus areas but suggest that they are too narrow. While each targets an important problem, they leave out the most significant causes of injury, death, and suffering among children in the United States today. We encourage funding research on the following areas and how these areas interact with each other: 1. Violence and Injury Prevention: Injury remains the leading cause of death in Americans age 1-44 years. In 2009, 73% of teenage deaths were caused by accidents, homicides, and suicides. Further, homicide is the leading cause of death among African-American adolescents and young adults, and nearly 5,000 youth were killed in homicides in 2012. Pilot studies show that these issues are preventable and some interventions have been effective. These include programs that provide summer jobs for adolescents, focus on social cognitive skills and self-awareness, and provide community-based mentors for young people. 2. Mental Health: According to a recent Agency for Healthcare Research & Quality (AHRQ) analysis, the highest cost medical conditions in childhood are mental health problems. The studies on adverse childhood experiences (ACES) demonstrate their high frequency and their clear impact on adult health. It is critical that ECHO focus on mental health and its co-morbidity with other medical conditions. Such studies should examine the effects of interventions across the life course. 3. Resilience: Finally, the four focus areas are all disease-focused. The National Research Council and Institute of Medicine Report entitled Children's Health, the Nation's Wealth emphasized the importance of focusing not only on illness and medical conditions but also on positive health development and resilience. Most children are healthy. Many live in difficult, stressful, or toxic environments. We must study how children respond to stress and poverty and why some children thrive in spite of adversity while others are broken by it.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

[Respondent] anticipates significant challenges in leveraging existing cohorts to collect standardized data elements as part of the ECHO program. Most existing cohorts are not expected to include all the necessary biospecimen or exposure data sought by the ECHO program; those that do likely cannot be readily analyzed together for infrequent outcomes. For endocrine disrupting chemicals (EDCs), we anticipate that existing cohorts will have dated exposure data that may not be relevant for the analysis of newly characterized EDCs or complex mixtures of chemicals. While we are encouraged by the program's objective to evaluate the maternal "exposome", we note that maternal and paternal exposures are extremely difficult to evaluate; therefore, active birth cohorts should be prioritized to ensure that maternal, paternal, and fetal exposures can be captured. We are not certain whether ongoing birth cohorts can be "retrofit" to ensure that data can be harmonized with other elements of the ECHO program. Additional RFAs may be required to ensure that cohorts are equipped to appropriately evaluate EDCs and other exposures. To efficiently manage resources, we suggest that the ECHO program leverage the proposed President's Precision Medicine Initiative (PMI) cohort.

Environmental factors, and in particular EDCs, should be considered in the context of this cohort. We anticipate rapid generation of large amounts of data through the PMI and other ECHO cohorts. Additional synergies can therefore be realized by connecting ECHO and PMI with the Big Data to Knowledge initiative. We recommend that basic scientists be well-represented in the planning, implementation, and evaluation of the ECHO program to strengthen the ability to discover fundamental, causal relationships between exposure and outcome.

Additional core elements to be considered

While linking exposure data to human clinical endpoints is of critical importance, we encourage NIH to incorporate data from animal studies to help establish the links between fundamental biology and clinical outcomes from environmental exposures. For example, animal studies can inform epidemiological studies, help researchers develop new or better biomarkers, or identify epigenetic changes that explain maternal or paternal exposures that affect children. We are particularly excited by the opportunity to identify and develop new biomarkers that show increased susceptibility to diseases later in life as a way to identify antecedents of human chronic diseases. Animal studies should also include collecting data from companion animals in addition to laboratory animals. There is a growing literature suggesting that dogs and cats are acting as sentinel species for endocrinopathies linked to EDC exposures. Given the proposed investment of significant resources over multiple years, it will be important to engage the biomedical research community and other stakeholders to ensure long-term support of the ECHO program. Researchers will need to understand the goals of the study and how it may relate to their research programs. Policymakers will need to understand why developmental origins of health and disease are important, and how chemical exposures are linked to human disease. Resources and data generated by the ECHO program should be easily accessible and widely disseminated. For these reasons, we encourage the NIH to develop a communication and community outreach plan associated with the ECHO program.

Considerations for harmonizing data across cohorts

[Respondent] believes that the ECHO program is an opportunity to help endocrinologists assess exposures to harmful contaminants and chemicals, in particular EDCs. Many EDCs would be expected to have biologically meaningful effects at very low levels, and chronic diseases that have been linked to EDC exposures, such as diabetes and obesity, may arise later in life. It will therefore be critical to develop strategies to ensure that the cohorts incorporated within the ECHO program collect data that can be aggregated, compared, and assessed over long periods of time and with sensitivity to low-dose effects, at least through puberty.

High impact areas of opportunity in addition to those listed

[Respondent] asserts that hormones are fundamental to all of the focus areas described in the Request for Information. Many endpoints and biological effects are mediated by hormone action, for example inflammation and oxidative stress, and we urge the ECHO program to evaluate the effects of exposures on hormone action. Additionally, there is a critical gap in our knowledge of the effects of exposures on developmental biology for people younger than 6 years of age. This age group is not covered by the National Health and Nutrition Examination Survey. This gap is an important area of opportunity that the ECHO program should address. By ensuring that environmental exposures to early age cohorts are measured, we can arrive at a better understanding of how exposures affect important developmental endpoints such as neurobehavioral function and IQ.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

[Respondent] is encouraged that the ECHO program anticipates implementing novel data collection and analytic methodologies. We anticipate that researchers will face significant challenges analyzing complex datasets generated by the ECHO program, including data on multiple types of exposures at different developmental time points. Indeed, there currently exists no robust method to statistically analyze mixture effects. We encourage NIH to issue targeted RFAs to statisticians to explore approaches to analyzing data generated by the ECHO program. The identification of new analytic techniques to assess mixture effects would have profound implications for toxicology and regulatory decision-making processes. The United States Environmental Protection Agency (EPA) should be engaged to ensure that repositories and data are collected in a systematic way that will be useful to the agency in risk assessments and regulatory decision-making processes. The EPA would be well served by resources that can better link epidemiological data to exposures.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

[Respondent] maintains that ensuring diversity in the ECHO program cohorts is essential to the overall success of the initiative. However, we recommend that NIH consider other aspects of diversity prior to establishing criteria for IDeA states based on geographic location. By incorporating diverse populations, specifically those populations that are underrepresented in clinical trials, the ECHO program could help advance the science of health disparities. We therefore encourage the NIH to make diversity and inclusion of underrepresented populations a primary consideration for the establishment of IDeA states.

Other Comment Provided in Attachment:

[Respondent] is encouraged by the goals of the ECHO program and we look forward to working with the NIH as the program is implemented. We stress that chemical exposures, and EDCs in particular should be a central theme of this important effort. These types of exposures are currently the most feasible to measure and should be prioritized in the early stages of the initiative. We note that the NIEHS has particular expertise in this area; we recommend that NIEHS maintain a leadership role in the ECHO program and be supplied with sufficient resources, both financial and operational, to ensure the success of this important endeavor.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

- Existing cohorts have established goals that may compete with those of the ECHO program. A challenge will be for existing cohorts to form collaborations with the ECHO program that are synergistic without undermining these established goals. For example, the Child Development Supplement to the

Panel Study of Income Dynamics would be highly appropriate study to include in the ECHO program because of its rich longitudinal, intergenerational, and intragenerational information and detailed contextual data. However, respondents have agreed to participate in a socioeconomic study, rather than a health study, and hence some caution may be necessary before collecting an expansive set of biological measures in a study such as this. • It is of utmost importance for the ECHO program to include population-representative cohorts rather than convenience samples. Population-representativeness provides the basis for generalizability of the program's research findings and avoids problems associated with self-selection and exclusion of certain population segments that might seriously undermine the scientific rigor of the results and their use in informing policy. • Another major benefit of the ECHO program focusing, perhaps exclusively, on population-representative cohorts is that the probability of selection in multiple different cohorts can be established. As a result, data that are pooled across cohorts can be reweighted to represent the union of all the component cohorts greatly strengthening the value of the data and findings. • Obtaining data through administrative data linkages—after receiving respondents' consent—provides an important avenue for enhancing existing cohorts while minimizing respondent burden. Linkages could be obtained with vital statistics birth records, medical records, schooling records, etc. However, the cost and effort involved in obtaining high rates of consent for individual linkages from respondents should not be underestimated.

Additional core elements to be considered

- The core elements should include a more comprehensive set of measures describing individual and family demographics. In particular, detailed indicators should be obtained for family income and wealth, employment and earnings, and parents' education. The collection of detailed prospective information on geographic location is key for establishing contextual exposures. Attention should be given not just to establishing contextual exposures based on residential location, but also on other locations within children's "activity spaces" where they regularly spend time—such as schools, parks, shopping centers, etc. Immigration status is a notable omission from the list of demographic elements. • The core elements should include measures that describe family characteristics and living arrangements that reflect the considerable degree of family complexity that children today experience. Many children grow up in blended households or divide their time between two households when parents separate or divorce, complicating the task of characterizing exposures at the household and neighborhood levels. • The core environmental factors should certainly include indicators of the social and economic environment—their omission from the list of examples is a major oversight. Many indicators of the social and economic environment could be obtained from external data sources through geocoded linkages (e.g., data from the American Community Survey). However, some other potential key indicators of the social and economic environment would need to be collected by trained observers (e.g., systematic social and physical observations) or by conducting complementary surveys of local residents (e.g., to quantify neighborhood social capital and collective efficacy). • There is an unfortunate lack of specificity in describing the four focus areas. Specifically, the "Pre-, peri-, and postnatal outcomes" that include "childhood outcomes" appear to subsume all of the other three focus areas. There needs to be considerable more clarity in describing and delineating the childhood outcomes that are to be considered.

Considerations for harmonizing data across cohorts

- Care should be taken to not impose specific harmonized measures on existing cohorts that might undermine their underlying goals and continued success. Rather, innovative approaches to constructing and validating "cross-walks" across different studies should be considered instead. • Harmonization will depend not just on the wording of the questionnaire items that are administered to respondents, but also to a great degree on survey mode, interviewer training, interview protocols and procedures, efforts

by interviewers to clarify questions to respondents and to minimize item nonresponse, respondent incentives, and the context in which interviews are obtained. The ECHO program would benefit greatly by drawing on the expertise of survey research methodologists and collaborating with them in designing and implementing the data collection protocols. • The role of the coordinating center in achieving harmonization should be considered carefully, because it represents a potential source of conflict as partner studies strive to meet their original goals and the goals of the ECHO program. Compromise and cooperation will be essential, particularly on the part of the coordinating center. • It is not clear how the coordinating center and the individual cohorts will share “ownership” of the data collected as part of the ECHO program. It would be essential for this issue to be thought through thoroughly before approaching specific cohorts for their participation in the ECHO program because of the potential sensitivity of these issues. It is not clear what is envisioned by having the data collection be “managed” through the Coordinating Center. Managing any single cohort is a complex and challenging undertaking, and an additional layer of external management from the Coordinating Center is potentially problematic in a couple of ways—first, in enrolling cohorts into the ECHO program and, second, avoiding conflict in the task of collecting data.

High impact areas of opportunity in addition to those listed

- The role of family dynamics and residential mobility in shaping children’s environmental exposures appears to have been given little consideration. However, these factors are likely to be crucial in understanding children’s actual exposures. In order to study these topics appropriately, it would be of high priority for the ECHO program’s component cohorts to collect detailed retrospective and prospective information about family change, residential mobility, and where children spend their time.
- Collecting detailed, high-quality data on family dynamics provides the basis for obtaining important information on siblings. In turn, data on siblings provides opportunities to control for shared family and contextual exposures while focusing on key differences in exposures and outcomes among siblings. The large and growing number of step- and half-siblings in American families provides further opportunities for obtaining new research insights.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

- Designing and implementing state-of-the-art data collection must directly address the pressing challenge facing surveys today which is the declining participation rates among potential respondents. The ECHO program may be able to effectively leverage the high level of interest in the study topic among potential participants. This will require the study to develop appropriate respondent materials and incentives, carefully-crafted interview protocols and procedures, and a toolbox of techniques to overcome respondent concerns and competing commitments. Collaboration with survey research methodologists and obtaining input from researchers on other surveys would be essential for obtaining high response rates and minimizing attrition.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

- An existing study that should be considered for the ECHO program is the Panel Study of Income Dynamics (PSID) and, specifically, the PSID Child Development Supplement (PSID-CDS). This study collects information on an on-going cohort of children. Beginning in 2014, the PSID-CDS design adds new children born into PSID families between each pair of waves, and hence provides a natural study in

which to examine prenatal exposures—particularly exposures associated with family poverty, food insecurity, and exposure to disadvantaged contextual environments. PSID-CDS currently includes a nationally-representative sample of 10,000 families and will add a refreshment sample of new immigrant families in 2017. There are approximately 5,000 children under age 17 years in PSID families, with about 300–400 newborn children added to the study each year. PSID collects detailed longitudinal data on the social and economic status and behavior of families. In addition, the study has geocoded longitudinal information on respondents’ residential locations that allow linkage with external contextual data. The study has run since 1968 and the sample has an enormously rich genealogical design that is built around adding adult children of original sample members to the study when these adult children form their own independent families. This genealogical design means that not only does PSID have a large number of siblings, but also a large and increasing number of first and second cousins. Furthermore, PSID is an on-going lifecourse study, and children who participate in PSID-CDS will be followed by the study for the rest of their lives. The PSID-CDS focuses on the collection of behavioral, developmental, and health outcomes, and includes the collection of cognitive assessments, time diaries, anthropometry, and saliva samples for genetic analysis.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

In Maine, there are several potential cohorts that could be leveraged: The Foundation for Blood Research in Scarborough, ME maintains blood samples that are currently being used for Autism research at Maine Medical Center Research Institute, and could potentially be used for research on other Focus Areas. Additionally, the Maine Medical Center Research Institute (MMCRI) maintains a Biobank, which contains human biospecimens with annotated clinical data from the Maine Medical Center Department of Pathology and the hospital’s Oncology Service Line. Nationally, each State’s public health department has a newborn screening laboratory that analyzes and stores blood samples from their newborn screening program (also called the “heel stick” or “bloodspot”). These blood samples could be utilized for genetic and/or other biomarker data as part of the ECHO program. An advantage of this cohort is that it is likely to be highly representative of the general population, since there are high rates of compliance with the screening program across the United States – in Maine, for example, state law requires all newborns to be tested with the newborn screening panel except when a parent has a religious objection to the testing. Additionally, the NCS collected longitudinal data from approximately 5,000 participants – leveraging this data as a cohort for the ECHO program would ensure this significant resource is utilized for its originally intended scientific purpose. One overall drawback of using existing cohorts is that most of these cohorts are unlikely to include underrepresented populations (e.g., racial/ethnic minorities) and therefore may limit the generalizability of study findings. However, Maine has the largest proportion of residents residing in a rural area (61.3%) according to 2010 U.S. Census data, so rural children would be represented in the cohorts described above. Embedding case control studies within the ECHO program would also increase the generalizability of study findings.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

Harmonization of data from different sources will be critical to ensure that existing cohorts from different studies are leveraged appropriately. [Respondent] has a newly implemented Epic-based Electronic Health Record (EHR) system, which allows for common data elements to be used. [Respondent's] Enterprise Reporting group and the Center for Performance Improvement have data analysts with considerable expertise in collating and extracting EHR data using a common data model. Additionally, investigators at the Center for Outcomes Research and Evaluation at [Respondent's] Research Institute have expertise in harmonization of data using EHR and large administrative claims based datasets, such as SEER/Medicare, as well as high-level biostatistics, bioinformatics, and epidemiological expertise. At the State level, Maine has a statewide health information exchange operated by HealthInfoNet, an independent nonprofit organization. This health information exchange links information from different health care providers to create a combined EHR that provides a linked health record for each patient, showing visits to hospitals, physician practices, independent laboratories, and other health care organizations. This health information exchange could be leveraged as a data resource for future ECHO research in Maine, and similar exchanges around the United States could serve as a significant data resource for the ECHO program.

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

There are opportunities to implement advanced data collection and analytic methods as part of ECHO. One potential resource that could be leveraged in this regard is the Observational Health Data Sciences and Informatics (OHDSI) program, an international research network comprised of multidisciplinary researchers focused on using large-scale analytics to generate evidence from observational health data. This open source collaborative uses observational health data from multiple sources and transforms the data using a standardized format, or Common Data Model. Researchers are then able to perform analyses on this standardized data using standard analytic routines written from the Common Data Model. OHDSI's Common Data Model can be used with both administrative claims data and EHR data, and could support collaborative, multi-institutional research as part of the ECHO program. Investigators at the Center for Outcomes Research and Evaluation at Maine Medical Center are active collaborators with the OHDSI program.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

In the Focus Area of neurodevelopment, Drs. Matthew Siegel and Susan Santangelo at Spring Harbor Hospital/MaineHealth are leading the Autism and Developmental Disorders Research Collaborative (ADDIRC), a national multi-site project that aims to develop a comprehensive registry of clinical and biological data on severely affected children and adolescents with Autism Spectrum Disorders (ASD). This project has just received renewal funding from the Simons Foundation and the Lurie Family Foundation, to continue the development of a unique autism cohort with high quality genotype, phenotype, and outcomes data. Additionally, Dr. Arturo Hernandez at the Center for Molecular Medicine at Maine Medical Center Research Institute has expertise in epigenetics and studies hypothalamic function and the hypothalamic-pituitary-endocrine axes. His work is relevant to a number

of disease areas, including autism and other neurodevelopmental disorders. Dr. Hernandez's lab could provide basic science expertise and resources to complement the clinical and epidemiological expertise of Drs. Siegel and Santangelo. The Foundation for Blood Research in Scarborough, ME maintains blood samples that are currently being used for ASD research at Maine Medical Center Research Institute, and could potentially be used to investigate other neurodevelopmental disorders such as ADHD. Maine has high rates of cancer incidence and mortality, in part due to high rates of tobacco use. Maine's smoking rate is higher than any other New England state with an average statewide smoking rate of 20%. In rural communities with low educational attainment and high poverty, smoking rates are estimated to be 40%. High levels of radon, a known lung cancer risk factor, also contribute to Maine's disproportionate cancer burden. The state Division of Environmental Health Radiation Control Program published data on the average radon level in each county, reporting that 10/16 counties had levels above 4 pCi/L (the EPA cutoff for mitigation).

The additional IDeA States opportunity

[Respondent] strongly endorses the proposed IDeA States National Pediatric Clinical Research Network. With 61% of its population residing in a rural area, Maine is well poised to evaluate health access problems and other health disparities among rural children. Additionally, Maine is currently experiencing significant increases in rates of obesity and opiate addiction – health conditions that affect children as well as adults. A recent CDC study found that Maine has the nation's highest rate of prescriptions for long-term, extended-release opiate medications. Consequently, there is increased incidence of mothers delivering opiate addicted babies in Maine. Drug addiction in newborns is also a national issue, so there is an opportunity to address a major public health problem through the proposed research network. The IDeA States network could link [Respondent's] clinicians and researchers with clinical trials experts who could collaborate to design new trials enrolling children and families in Maine, to begin to address gaps in access to care and prevention, and/or interventions aimed at opiate addiction. A multi-center trial enrolling drug-addicted newborns could be formed to create a new cohort that could be followed longitudinally, to examine long-term outcomes of individuals who are born with substance addiction. The IDeA States research network could also build on existing resources, where appropriate. One such resource in the area of obesity is the "Let's Go!" program of [Respondent's] parent health system, MaineHealth. This program – which is based in Maine but is also being implemented in other states – focuses on preventing childhood obesity by partnering with daycares, schools, and other institutions to provide education and resources on healthy behaviors such as exercising and eating fruits and vegetables. This program has gained national recognition and served as a model for the childhood obesity prevention initiatives of the American Academy of Pediatrics.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

There may be some issues trying to collect these core elements pre (peri-)conceptionally or prenatally in extant time-to-pregnancy cohorts. Each one of these windows are limited in duration. Women get pregnant (the most fertile most quickly) and have babies, thus limiting your window of eligibility or time to approach them. If you wanted to use previously collected samples, that might work; however, they would not then necessarily have all core elements. However, you could add on additional follow-up of the offspring. Another option is to identify cohorts as they are funded, prior to implementation. This would be an ideal time. An additional award could be provided to add the core elements. However, you

would need to walk a fine line, as you certainly would not want to interfere with achieving the specific aims of the originally funded project. A third option, would be to use sites that have existing cohorts, but “extend the life” of the cohort. By that I mean add the new protocol components to the existing protocol for the cohort. However, the site would continue recruiting beyond the planned sample size of the original cohort. Upfront, it would need to be clarified which data would go to the coordinating center. Finally, you could simply recruit sites that have had such cohorts and likely have maintained the infrastructure.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

In general I am excited to see that the NICHD seeks to address some of the very important aims of the Children’s study. I do think that there should continued focus on the impact of peri-conceptual exposures on child health and development. I think the idea of assessing the core-elements preconception, prenatally, and in early childhood is an excellent one and you may need a number of cohorts (some pre-conception, some prenatal, some early childhood) to meet achieve your goals. Leveraging the experience of sites with extant cohorts, seems like an excellent idea. Please see my concerns regarding leveraging extant cohorts.

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

Time to Conceive has enrolled nearly 850 women from the community, who desired to conceive, and obtained blood and urine and various survey data from the women. Participants are actively followed throughout their attempts to conceive over the following twelve months. During that time, women conduct standardized pregnancy testing and complete a daily and monthly diary for collection of detailed exposure data. Pregnancy follow-up includes ultrasound assessment for viability and a pregnancy outcome report including obstetrical and neonatal information. Further offspring follow up is not currently being conducted at this time, but I assume this could be a possibility

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect

standardized data elements

The idea of building on existing cohorts rather than beginning an entire new data collection effort is a reasonable approach as long as the cohorts chosen are not narrowly focused. The NIH panel convened regarding the original National Children's Study and the IOM emphasized the need to use probability-sampling methods to ensure that the results of such studies could be generalized for the entire US population. Clinic-based samples are typically not sufficiently representative to allow for such generalizations. There are a number of nationally representative surveys that include large samples of children who have been and are being continuously followed over time. These samples provide rich data not only on socioeconomic characteristics of the families and households but in some cases they also include biomarker data. In addition, these surveys can be geocoded to characterize the residential context where these families have been and are currently residing. It is critical that at least some of these nationally representative samples are included among the cohorts to be selected by NIH for the proposed study. These data include among others: The National Longitudinal Study of Adolescent to Adult Health (Add Health) - <http://www.cpc.unc.edu/projects/addhealth>; the various National Longitudinal Surveys (NLS), including the child supplements of the children of the participating respondents (<https://www.nlsinfo.org/>); and the Panel Study of Income Dynamics and its child supplements (<https://psidonline.isr.umich.edu/>). It is critically important to include these types of nationally representative cohorts among the cohorts chosen for the proposed study.

Additional core elements to be considered

In addition to health related data, the socio-demographic context over the life course is critical for understanding the multiple factors and their interactions that contribute to child development, health outcomes early and later in life as well as mental health over the life course. Thus environmental influences need to be broadly defined from the family environment, including family, household and housing characteristics, to the social and physical neighborhood context. Demographers, sociologists, economists and other social scientists have spent considerable effort in devising measures that adequately capture the complex social and political environments where the children and their families are embedded. Many of these measures are already incorporated into the various longitudinal cohorts that I mentioned above. It would be important to integrate these types of measures to all cohorts included in the proposed new study in consultation with experts familiar with the collection of such data in nationally representative samples.

Considerations for harmonizing data across cohorts

It is important that key data elements, including those that capture the demographic and social environment at the family and neighborhood level, are harmonized across all cohorts. It will also be important to have a nationally representative sample with the same data elements, so that it will be possible to assess the representativeness of the more specialized, clinic-based cohorts against nationally representative samples. The development of such harmonized measures would be aided by building upon existing data collection instruments.

High impact areas of opportunity in addition to those listed

The incorporation of health data, biomarkers and genetic data with a rich set of sociology-demographic and environmental data should enhance the ability to examine possible important interactions among these determinants of child development and health across the life course. Such examination will, however, require rich well-designed data collection instruments on all dimensions.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

It may be possible to implement innovative data collection methodologies across multiple platforms, including the Internet and various hand held devices. However, such data collection requires testing of the impact of the data collection mode on data quality and ability to maintain nationally representative samples. Much could be learned from various governmental agencies and non-governmental organizations that have used multiple modes of data collection, e.g., the Census Bureau, National Center for Health Statistics, Survey Research Institute at the University of Michigan, Add-Health et cetera.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

All are nationally representative longitudinal samples: The National Longitudinal Study of Adolescent to Adult Health (Add Health) - <http://www.cpc.unc.edu/projects/addhealth>; the various National Longitudinal Surveys (NLS), including the child supplements of the children of the participating respondents (<https://www.nlsinfo.org/>); and the Panel Study of Income Dynamics and its child supplements (<https://psidonline.isr.umich.edu/>).

The additional IDeA States opportunity

No Response

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

APA supports the attempt to put together a very large, representative sample that, due to the use of existing cohorts, will minimize the costs of recruitment. We are concerned, however, that there may be difficulties in making these studies, which were designed for other purposes, yield information consistent with ECHO's goals. Thus, the quality of the outcome will likely be based on the quality of the samples and studies chosen, as well as the abilities of the investigators and research community to integrate the data in ways that address the questions needed to inform public health.

Additional core elements to be considered

We appreciate the broad range of core elements to be considered across the studies, especially the inclusion of environmental and psychosocial factors. It may also be important to explicitly include a mention of environmental factors that contribute to resilience and enhanced social/behavioral and intellectual/cognitive development and functioning to complement the focus on impairment in these areas.

Considerations for harmonizing data across cohorts

If the samples chosen are too small, even with rich, dense longitudinal data, it could be extremely difficult to weave a number of these smaller studies together to form a cohesive, functional, and representative data base. Having a representative sample is important not only to be able to answer the central questions of ECHO, but also key to evaluating health disparities in traditionally underrepresented

racial, ethnic, and low socioeconomic status populations, and in populations of individuals with disabilities. Thus, NIH may want to specify in the funding announcements that it only aims to involve large, representative extant studies (e.g., greater than 10,000); this will also reduce the burden on review. NIH could also consider a two-step process whereby it initially selects extant studies based on size and quality of the designs. Then once selected, NIH could invite proposals for integrating these data sets into larger data sets to produce truly nationally representative samples that can capture environmental exposures, as well as address the core elements and research questions specific to childhood health outcomes.

High impact areas of opportunity in addition to those listed

We are encouraged to see the inclusion of neurodevelopmental issues among the four focus areas. Although we recognize that the list of neurodevelopmental issues is not exhaustive, we suggest adding intellectual disability to the list of conditions included in any further informational or funding announcements.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

APA expresses its hope that topical expertise is sought out to yield consensus on study instruments, batteries of assessments, and outcome measures in order to quantify constructs of interest, especially to assure robust measurements of psychological and behavioral phenomena. Additionally, instruments and measures appropriate for traditionally underrepresented populations and individuals with disabilities should be identified. Thus, APA strongly suggests that expertise in the social and behavioral sciences be retained in the ECHO Coordinating Center, Steering Committee, and any related advisory groups and program offices.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)
(*Submitter left answer blank*)

The additional IDeA States opportunity

(*Submitter left answer blank*)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Congress has reaffirmed its support for the mission of the National Children's Study: that of identifying environmental exposures that impact children's growth and development. The key features of this vision are the fact that this work is to be conducted with an eye towards understanding the exposures that influence children's health in the United States and that, in approaching this as a cohort study, the impact of these exposures can be measured on a wide variety of potential outcomes, ranging from those developing in early childhood to those that provide the seeds for chronic diseases in adults. This approach provides its efficiencies only when well-designed exposure assessment throughout pregnancy

and childhood is paired with the high quality outcome assessments. Other designs, such as case-control studies, are much more efficient for understanding the etiology of specific outcomes. Therefore, in looking towards ways to support the NCS's mission, it is key to examine the ability of the proposed design to support a cohort with well-characterized prenatal exposures. Unfortunately, most extant cohorts are limited in this regard. Specifically, it is insufficient to rely on recall, existing records or environmental sampling to provide the individual-level exposure assessments that provided the foundation for the NCS. Even if the existing cohorts could provide high quality outcome data and could retrospectively gather information on a variety of exposures, it is likely that concerns about ecologic fallacies and exposure misclassification would remain. Further existing cohorts have been developed with specific goals and hypotheses in mind. Therefore, it is unlikely that a compilation of such cohorts, assembled with a focus on various hypotheses, would systematically include the full array of exposures and outcomes that would be provided by developing a novel, nationally-representative cohort such as was proposed in the NCS. .

Additional core elements to be considered

One potential advantage of the approach proposed in the NCS-A: the extant cohorts are likely to represent children who have been born at a wider variety of time points than is likely to be possible if assembling a new cohort. Thus, to these extent that there are secular trends in exposures, the assembled cohorts would have the opportunity to are currently a variety of ages, and to the extent that these exposures are changing over time, these cohorts could then observe secular trends in these exposures

Considerations for harmonizing data across cohorts

Two factors are key when harmonizing data across cohorts: there must be similar exposure and outcome data. The latter is relatively simple and as these cohorts, by definition have a prospective component and are likely to include information clinical diagnoses using standard or care, it is likely that it is relatively straightforward to assess these in a similar manner across cohorts. However, it is likely that these diagnoses do not represent all possible outcomes, and that these outcomes are not assessed similarly across all populations. For example, in relying on data on intellectual disability, it is likely that some cohorts will need to rely on diagnoses made within educational settings. These diagnoses are unlikely to be made on all children, and there are likely to be substantial differences in which children are tested and which tests are used across different areas. These differences are also likely to vary by important risk factors such as socioeconomic status – and which are associated with environmental exposures. Harmonizing data on environmental exposures in pregnancy offers a much more difficult problem. Specifically, providing a standardized set of data on early exposures would require retrospectively collecting data from available records. These would be limited in their scope. For example, air pollution data are available in some urban areas but likely not in rural areas. Additionally, even when these data can be obtained for a large number of cohorts, use of these data is likely to result in substantial nondifferential misclassification which is going to result in significantly reduced power to identify true exposure-outcome associations.

High impact areas of opportunity in addition to those listed

I think the keys to choosing high impact areas include: Exposure-outcome relationships in which a relatively large, but not enormous sample size is needed, the presumptive exposure is early in life (including intrauterine life), and the outcome develops or is diagnosed later in childhood (preschool or later) because other relationships could be examined via other mechanisms. For example, the etiology of preterm delivery could be examined much more efficiently using a smaller cohort followed for a shorter period of time. Additionally, outcomes that are of high impact, and those with increasing

incidence, should be prioritized.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

[Respondent] strongly supports the study of the effects of preconceptional and gestational environmental exposures on pregnancy outcomes and child development. Such investigations should be conducted in a well-defined, systematic manner that has a high likelihood of yielding meaningful data.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

IDeA States opportunities Address access gaps for rural children through a national network for pediatric research embedded at IDeA locations. 1. Telemedicine technology has demonstrated improvements in access, especially in rural areas, and IDeA states have been leaders in adopting this technology. However, major gaps exist in the comprehensive evaluation of a complete tele-health system and strategies to improve patient outcomes in large populations. Effective research will require collaboration between patients, especially in rural areas, health care providers, policy makers, social scientists, engineers, economists and government agencies. A national IDeA State Network to address major access issues with a focus on post neonatal mortality could ultimately lower infant mortality and provide the impetus to enhance access for underserved populations. Link existing IDeA state centers with experts in clinical trials 2. The high Infant Mortality in the US is a “national embarrassment” (Washington Post). The southern IDeA states have traditionally had the highest infant mortality in the US, exceeding the national average by 50%. Excess infant mortality can be traced to increased preterm delivery, especially in rural and African American populations. We propose a multi-state study to identify environmental, genetic and demographic data associated with preterm delivery among rural and African American women. Findings will be used to inform intervention strategies for prevention and treatment of preterm delivery.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) established the “Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b)” in 2009. The overarching goal of this prospective observational study of nulliparous woman was to study mechanisms for and prediction of adverse pregnancy outcomes (APOs), including prematurity, preeclampsia, and intrauterine fetal growth restriction. The Network enrolled and followed over 10,000 racially, ethnically, and geographically diverse women from early pregnancy through delivery (enrollment 10/2010–9/2013; last delivery 5/2014). The study included collection of socio-demographic factors (including residential address at four time points during pregnancy for geocoding); maternal nutritional, behavioral, and psychosocial assessments; clinical and sonographic measures; maternal and neonatal outcomes; and maternal, fetal, and placental specimens. A longitudinal substudy of sleep disordered breathing in over 3,600 women was conducted to estimate prevalence during pregnancy and to study association with APOs. The National Heart, Lung and Blood Institute (NHLBI) and NICHD subsequently funded a follow-up of the women to determine the impact of pregnancy findings and outcomes on health following a first pregnancy, and on subsequent pregnancy outcomes. This ongoing follow-up began 10/2014. To date, over 5200 women have participated in 6-month interval contacts via telephone interviews or online questionnaires; over 1500 eligible women have attended clinic visits; and approximately 450 eligible women have had sleep studies following the clinic visits. Follow-up of the children from the nuMoM2b cohort is an opportunity for the ECHO Program to leverage the richly characterized phenotype of these children’s initial environments beginning in early pregnancy; and the ongoing interval contacts with the mothers allows for easy-access to the children as a whole and for targeted substudies. Furthermore, the materials and systems are available for further enrollment to nuMoM2b (for example, through IDeA state centers), if needed, to increase cohort membership or to enhance diversity.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

We are encouraged that neurodevelopmental disorders will be a major focus of the ECHO study. Undoubtedly, prenatal and perinatal exposures are important causes of non-optimal brain development, but for many disorders such as autism, ADHD, and schizophrenia, there is a latency of months or years between the neurodevelopmental insult and clinical diagnosis. Moreover, environmental exposures act in the context of genetic vulnerabilities, and hence even prospective assessments of obstetrical, neonatal, and postnatal variables need to take genetic variability into account. Moreover, at the level of an individual child, the neurodevelopmental consequences of environmental insults will depend on moderating variables later in life.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

At Emory University and Children's Healthcare of Atlanta, [Respondents] are working with Karlene Coleman and Lisa Kobrynski et al. on various studies of genetically high risk individuals who have the chromosome 22q11 deletion syndrome (22q11DS). This is a genetic disorder that associates with 14-50% risk for autism spectrum disorder, and 20-30% risk for schizophrenia. Because there are prenatal and neonatal antecedents of the adverse neuropsychiatric manifestations of 22q11DS, we are examining obstetric and child health variables as risk factors for later psychiatric diagnosis. We have established a database of over 700 individuals with 22q11DS, and are populating it with over 4000 fields of medical record information. Emory specialty clinics facilitate long-term contact with these patients as they progress through childhood and into adulthood. Dr. Walker also directs one of nine centers participating in the North American Prodrome Longitudinal Studies (NAPLS), which is a longitudinal cohort of children and young adults at high risk for psychosis. The first phase of NAPLS has obstetric data reported by the mothers of these participants, and NAPLS-2 has 1045 cohort members (135 at Emory) who are mainly in

their reproductive years. This provides a unique opportunity to examine second generation effects in concert with longitudinal parental psychosocial information.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

There is considerable benefit to leveraging existing cohorts to collect standardized data elements, including benefits related to cost and minimizing infrastructure development. Drawbacks include lack of currently important information – cohorts that were previously collected may not include all variables of interest for current projects. Conflicts between data collection sites will have to be managed. Pro-active and clear guidelines would be critical – for data use, publication, etc. Overall, these drawbacks can be managed and only sites willing to agree to guidelines should be included.

Additional core elements to be considered

The core elements could be expanded to specifically address a critical neurodevelopmental concern, namely the effects of prenatal alcohol exposure. This exposure affects as many children in the U.S. as ADHD and autism but research in this area is significantly underfunded. Specifically, the core elements regarding epigenetic influences on child development and environmental factors could be expanded to include prenatal alcohol exposure.

Considerations for harmonizing data across cohorts

As part of the Collaborative Initiative on Fetal Alcohol Spectrum Disorders... data are collected from multiple sites and in multiple domains of assessment. For this project children are assessed using neuropsychological and behavioral tools as well as brain imaging, genetic, and dysmorphological evaluations. Thus, we have considerable experience with cross-site/cross-domain data collection. Data collected in this manner presents unique benefits and challenges. For example, increased heterogeneity results in greater variability but also provides a more generalizable picture of important outcomes. Special consideration needs to be given to reliability of data collection methods, training and continued monitoring of research staff, and centralized data storage.

High impact areas of opportunity in addition to those listed

Focus areas specifically mentioned include pre-, peri-, and postnatal outcomes (e.g., birth defects, childhood outcomes) and neurodevelopment (e.g., autism, ADHD, depression, social/behavioral development, cognition). These are critical areas that deserve research focus. In addition to these, and directly related, is research on the effects of prenatal alcohol exposure. As has been made clear by multiple research studies, including my own, the effects of prenatal alcohol exposure are devastating and life-long. They include effects on brain development, cognitive, behavioral, and social development. Fetal alcohol spectrum disorders (FASD) affect as many children as ADHD but are very often unidentified or misidentified. Critically, research in this area is grossly underfunded in comparison to other developmental conditions like ADHD and autism.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

... the Center for Behavioral Teratology (CBT) at SDSU and ... the NIAAA-funded neurobehavioral assessment project of the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) ... access to unique cohorts of subjects. Though research at the CBT was not designed to be longitudinal, I have been researching FASD at the CBT for over 20 years and have a database of 100s of children who have participated in our studies. CIFASD is a multi-site study, including the CBT, and is currently in its 11th year (funded through 2017). Recruitment has focused on subjects with the following characteristics: - Children with histories of prenatal alcohol exposure -Children with attention-deficit/hyperactivity disorder (ADHD), other externalizing or internalizing behavioral concerns or conditions, or learning problems -Typically developing children without prenatal alcohol exposure or behavioral/cognitive concerns Data collection methods: Children have been assessed using neuropsychological measures (direct child measure) and parent questionnaires. Some subjects also participate in other CBT and CIFASD projects, including brain MRI, genetic testing, dysmorphology, and 3D facial imaging. Sample size and demographics: The current phase of CIFASD (phase III) has recruited and tested 600 subjects. These children are 5-7years or 10-16years of age. They are approximately 45% female, 15% Hispanic, 48% White. Over 800 subjects are planned for this phase. Phase II recruited over 750 subjects at multiple sites The CBT database includes over 250 active subjects with the following characteristics: These children are approximately 38% female, 32% Hispanic, 25% Race Non-White. We keep in touch with these subjects through follow-up letters every 6 months. Relevant to the overall goals mentioned previously, over 60% of subjects with alcohol exposure meet diagnostic criteria for ADHD and rates of other conditions, such as oppositional defiant disorder, conduct disorder, anxiety and mood disorders, are also elevated.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Agricultural Health Study (AHS) is a prospective cohort that includes 54,000 farmers and 32,000 of their spouses who were enrolled in Iowa and North Carolina from 1993-1997. Since then, three follow-up questionnaires have been administered focusing on agricultural exposures, including use of specific pesticides, lifestyle factors (alcohol, smoking, physical activity, BMI), medical conditions and medication use, other occupational exposures, and some dietary information. Buccal cells were collected from approximately 45% of the cohort and the residences have been geocoded for linkage to environmental databases. This unique cohort has provided numerous insights into chronic diseases in rural and agricultural populations, including how early life exposures may impact adult disease risk (Hofmann et al. 2015). A subset of AHS participants provided information on their children. To date, 38,000 children born from 1975-1999 to AHS cohort members have been identified in Iowa through self-report and linkage to the Iowa Birth Registry. These data have been used in previous studies of cancer incidence and all-cause mortality among this group in relation to parental exposure information, demonstrating increased cancer risks and mortality due to injuries (Flower et al. 2004; Flower et al. 2007). These data are currently being updated with 12 additional years of follow-up. The oldest members of this group of offspring who were born and/or who grew up on farms are now entering their fourth decade of life, and represent a unique opportunity to evaluate early life exposures on subsequent disease risk in childhood and early adulthood. By contacting offspring directly, researchers could obtain updated medical and exposure histories, including pesticides and other farm exposures, and combine these data with the information from their parents during critical windows of exposure. Additionally, biological material such as buccal cells from this group would allow investigation of several hypotheses, including transgenerational effects.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

We propose that a clearinghouse be established that lists available databases and sample banks from completed NIH-funded studies involving women and children. Guidance and assistance could also be provided to independent investigators for obtaining access to answer research questions. A mechanism for ongoing support and protection of sample banks (for a finite time period) ought to be considered, as well. Insights from our laboratory's participation in an NICHD-funded study in 2005 prompt this

proposal. At that time, our laboratory measured TSH, free T4, and TPO antibody levels in 23,000 serum samples from the first and second trimester evaluation of risk... Those measurements, coupled with demographic, biophysical, and pregnancy outcome information, led to a series of analyses and publications that continue to yield valuable insights into relationships between maternal thyroid function and several complications of pregnancy and delivery. At the end of the ... trial, no finances or standardized storage policies were available to maintain the serum bank. In spite of this, the decision was made to store the sera, but the contents of an entire freezer were subsequently lost after an unalarmed storage unit malfunctioned. The NIH Stillbirth Study represents another example of where attention and monitoring from a clearinghouse might avoid long delays in accessibility to the database and stored samples. Several years have elapsed since the study's end, and the data are still not available.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

Obesity, Nutrition, Diabetes In 2005, our laboratory measured TSH, free T4, and TPO antibody levels in 23,000 samples from the first and second trimester evaluation of risk (FaSTER) dataset ... Those measurements, coupled with demographic, biophysical, and pregnancy outcome information, revealed a link between free T4, obesity, and gestational diabetes. Women in the highest BMI range had relatively low T4 levels and an increased risk for developing gestational diabetes. One mechanism to explain this relationship is that peripheral deiodinase activity (PDA) increases in obese/heavy weight women. PDA refers here to deiodinase-1 and -2 activity in the liver, muscle, and kidney that converts T4 (inactive precursor) to T3 (active hormone). Published data by us and others document not only an inverse relationship between BMI and T4 (as in our dataset), but also a direct relationship between BMI and T3. The T3/T4 ratio serves as a surrogate measure of PDA. Higher T3/T4 ratios during pregnancy (increased PDA) have been shown to be associated with higher maternal BMI, as well as increased hemoglobin A1C and insulin levels, and larger weight placentas. We propose a cohort study in euthyroid pregnant women receiving routine care at our institution to explore the extent to which higher BMI stimulates peripheral deiodinase activity which, in turn, contributes to hyperglycemia, insulin resistance, gestational diabetes, and birthweight. Our recent pilot study has established the feasibility of obtaining plasma samples, biochemical, biophysical, demographic and outcome data from 8,000 women being screened for gestational diabetes at 24-28 weeks' gestation. Presently, nearly all thyroid studies dealing with pregnancy address adverse events arising from malfunction of the thyroid gland itself. This

proposal broadens the scope of investigation to include PDA as a model for monitoring environmental influences that may not only impact fetal/postnatal growth and development but also be amenable to modification.

The additional IDeA States opportunity

Rhode Island (an urban/suburban state) and Maine (a sparsely populated rural state) are both IDeA states, and both are economically disadvantaged with underserved populations. Given their geographic proximity, it would be reasonable to combine resources from both states to address a common problem with the potential to involve basic/clinical scientists, students, public health departments, universities, and others. We propose a thematic approach with gestational diabetes as a focus that includes glucose metabolism, obesity, thyroid/deiodinase function, metabolic syndrome, adverse events of pregnancy/delivery, and long term consequences to the offspring. Pregnancy can be viewed as a metabolic stress test that could offer insights into immediate and longer term health implications for both mothers and children. In addition to laboratory-based and epidemiologic investigation, innovative strategies for improving glucose management, such as use of resins, could be evaluated in randomized trials.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

We believe that an RFA encouraging new prospective studies in more complete alignment with the Core Elements and the Four Focus Areas, as described in the Request for Information, is a better long-term strategy for the investment of NIH funding. However, we recognize that the prospect of leveraging existing cohorts, data sets and tissue banks could provide new medical insights, even if they do not include all of the Core Elements or address all of the four Focus Areas. A critical element in such an approach would be the compilation of a national directory of information on the types of Core Element data and outcome measures that could be made available as a primary resource for use by various organizations to develop proposals on how merging datasets would advance knowledge in ways not possible by examination of separate independent datasets. Specifically, a Central Data Repository with standardized data dictionary, validation, and QA/QC processes would be required to comprehensively assess the effect of prenatal exposures on proximal and distant pediatric outcomes, birth cohorts with comprehensive pre-, antenatal and postnatal assessments.

Additional core elements to be considered

We agree that the RFA should include an emphasis on environmental exposures as one of the four Core Elements. We strongly recommend inclusion of alcohol, nicotine, heavy metals, illicit drugs, and pharmaceutical agents with known or suspected teratogenic potential. We also recommend that both a maternal and neonatal “exposome” should be considered in parallel, but the manner in which this large volume of information would be correlated with other Core Element data and the Focus Area outcome measures must be specified.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

As suggested in the RFI, we agree that addressing specific needs of rural children is a big opportunity. Connecting pediatric research centers in IDEA states is a logical way of doing this.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

We agree that a new prospective study should include the establishment of more comprehensive, state-of-the-art tools for general screening of pregnant women and infants (combinations of self-reported data, bio-monitoring and environmental assessments) that could lead to more targeted screening protocols for discerning risk for specific diseases related to the Four Focus area.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

In the spirit of the original National Children's Study, we concur with the RFI's identification of four Focus areas that could be more practically implemented in a prospective "downsized alternative NCS" study, for the following reasons: 1) Collectively, these four areas constitute a large proportion of the health burden in the pediatric population. 2) The time frame for conducting a systematic investigation that correlated the Core Elements with these four Focus Areas could be accomplished in a ten-year project period. 3) There already exists networks of centers focused on neurodevelopmental disorders, asthma and obesity/diabetes, that could facilitate the implementation of such studies.

The additional IDeA States opportunity

We strongly endorse the prospect of developing an IDeA States National Pediatric Clinical Research Network. Currently, there is no NIH mechanism for pursuing such an opportunity. As implied in the RFI, addressing the specific health challenges of rural children, given the health disparities associated with this population, is a critical unmet need. The RFA could be a tremendous opportunity and a logical way for connecting health research centers in IDEA states. Currently, there is established infrastructure that is connecting basic scientists, clinical and community investigators across IDEA states and between IDEA states. Leveraging this for pediatric outcomes research makes a lot of sense. In many respects, the investment of funds for an ECHO program in an IDeA network of pediatric research centers with experts in clinical trials research could have a far greater long-term impact on health outcomes than investment in other venues.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Birth cohorts have contributed enormously to the prevalence, natural history and risk factors associated with common non-communicable diseases such as asthma. Cumulatively, there are hundreds of years of investment in the existing cohorts, resulting in the collection of vast amounts of information. It is clearly in the interest of science and human health to take advantage of the data and samples that has already been collected to answer key research questions. Standardization of already collected data is possible to some extent. When the cohorts come together, there is also the opportunity to standardize future

collection of data. I would also suggest looking beyond the US and include cohorts from other countries where there is an existing collaboration with US investigators. Europe, and especially the United Kingdom, has a number of cohorts with a wealth of information and rich sets of data. There has recently been a concerted effort in bringing the US and European cohorts together. NIH organized a workshop in 2014, which provides further impetus to this effort (Bousquet et al. *J Allergy Clin Immunol* 2014;133(6):1535-46. Some cohorts based outside of the US have a significant input by US investigators investment by NIH. As these cohorts have information that may not be available in the US, I suggest including these cohorts in future research initiatives. There are some drawbacks in the utilization of existing data such as non-standardized format, variance in the way data has been collected in different cohorts and the time versus cohort effect. For instance; has the environmental exposures changed over the last decades so that the historical cohorts may not now be relevant? This is unlikely, although it can be argued that a major part of any future efforts should be to include cohorts of different ages, to provide a comprehensive picture.

Additional core elements to be considered

The power of cohorts comes from the longitudinal collection of data. This means that causality can be assessed with sequential information on environmental exposure e.g. during prenatal and post-natal period and health consequences that follows. In this context, multi-generational cohorts are uniquely important as the investigation of environmental exposures during pre-natal period require at least two generations. Indeed, recent reports indicate that grandparental exposures such as tobacco smoke, could influence childhood health outcomes in their grandchildren. Thus, seeking multigenerational cohorts, where information is available on 3 or more generations would be particularly useful. This transmission of "information" across generation is likely to be conveyed through epigenetic mechanisms. Thus, a particular emphasis in existing and future cohorts should be on understanding epigenetics.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

Including allergies and immune responses as a distinct focus is suggested. Allergic diseases are extremely common with nearly 25% of the population suffering from one or more of these conditions. Allergic mechanisms are critical in the normal development of airway function and have long term effect on chronic conditions such as asthma. There is also a wealth of information on allergic diseases in existing birth cohorts that can be immediately available.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

Collection, storage, harmonization and utilization of data collected over several years by different cohorts are challenges that require special expertise and experience. We, in Europe, have significant experience of birth cohort consortia that have attempted to do just that. These include Study Team of Early Life asthma Research (STELAR, UK) and Mechanism of Development of ALLergy (MeDALL). The anticipated advances relate to the technological and computational development in storing, accessing and analyzing large amount of data through internet and freely available software. Within the STELAR consortium we have developed "Asthma eLab" with the computing power to match the available wealth of data collected over 20 years in over 12,000 participants. Similarly, in the MeDALL consortium, data has been combined and being analyzed for over 20,000 participants. These efforts require specific expertise and the coordinating center will be required to seek help from the epidemiologist and biostatisticians.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Isle of Wight (IoW) birth cohort (n=1,456) has been extensively assessed for environmental exposures and respiratory health outcomes at birth and ages 1, 2, 4, 10, and 18 years with over 80% participating throughout and objective assessments such as lung function and bronchial hyperresponsiveness at age 10 and 18 years. Information on pre-natal exposures includes pregnancy conditions, maternal risks such as obesity, smoking, pet exposure, and housing characteristics and maternal serum has been collected and stored. Assessment at the age of 26 years of this cohort is ongoing to determine respiratory health, allergic conditions and obesity related health outcomes. The biological samples currently available include serum/blood samples at birth, 10 and 18 years, induced sputum and bronchial biopsy in a subset. The cohort has contributed significantly to prevalence, natural history and risk factors for allergic diseases with over 100 publications. The Isle of Wight cohort is a shining example of how UK and US investigators could work together, taking advantage of their respective expertise, for betterment of human health. The cohort participants have volunteered the next generation (their children) to be recruited in a study focusing on transgenerational epigenetic mechanisms (funded by the NIAID). These children are being assessed for pre- and postnatal exposure including microbial flora in the gut, skin, nose and environment. This cohort, with its longitudinal phenotyping and extensive samples in three generations, provides a unique opportunity to investigate the influence of environmental exposures with an emphasis on pre- and postnatal exposures and childhood health outcomes.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Appropriately designed animal studies are important to complement studies done with human cohorts. They will provide access to materials not available in human studies, which are necessary for mechanistic insights. For example, in assessing epigenetic mechanisms by which environmental factors influence neurodevelopment, it will be necessary to perform epigenomic analyses on brain tissues across the life course. This will not be readily achieved if studies are limited to use of extant human cohorts.

Additional core elements to be considered

Nutrients should be among the biological and chemical environmental factors influencing all four focus areas, and not just as variables affecting obesity. Proper neurodevelopment and function depends vitally on nutrients, some of which might have sub-optimal intakes across the population.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

The goal of identifying the “seeds” of future diseases and conditions is important; so is the goal of maintaining health through habits and interventions that prevent those seeds from arising and germinating. Disease ontology and health optimization are related but distinct endeavors, which both require attention and resources.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

When applying epigenomic approaches to studies of Environmental influences on Child Health Outcomes, it is important to account for variations in cellular composition of materials analyzed as part of those studies. When environmental exposures alter cellular composition of relevant tissues, epigenomic features associated with different exposures might be secondary to the cellular composition differences. These will be of less importance to mechanisms important for health and disease states, than epigenomic differences within a cell type.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDEA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

There are significant benefits to leveraging an existing cohort besides likely reduced funding costs and time needed for recruitment. A well characterized cohort will have collected early markers of development and accumulated sufficient longitudinal data for analysis in the near term, as opposed to having a prolonged lag time to collect outcome data in a prospectively newly recruited cohort. Drawbacks may include either data limitations on specific elements of early life environmental factors in a retrospective cohort or recall biases if attempting to collect additional early life data in a retrospective cohort.

Additional core elements to be considered

We would also consider the collection of genetic information in at least some cohorts as environmental and epigenetic changes may be influenced by genotype (e.g., gene-environment interactions). Again, using an existing cohort with genetic data may reduce study time and costs. In addition, the use of geographic identifiers can also for conducting sophisticated geospatial analyses to capture macro-environmental exposures such as air pollution, traffic, climate, socioeconomic status, etc.

Considerations for harmonizing data across cohorts

Although obviously standardization is extremely desirable, particularly with respect to the core elements, some diversity among the cohorts among other data elements may be beneficial to serve as test beds for new analytic tools or more expensive data collection, such as epigenetic testing of specific gene(s) or overnight polysomnography.

High impact areas of opportunity in addition to those listed

The use of family-based studies should be considered as these cohorts may allow for the parsing of genetic versus environmental contributions to critical pediatric conditions. In addition, while the collection of data on common pediatric conditions (e.g., asthma) is extremely important, consideration should also be given to well-circumscribed monogenic diseases. Environmental and/or epigenetic effects may be easier to detect in individuals with a common genetic backdrop of disease.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

Geographic information systems (GIS) advances will continue to expand to provide additional data on a variety of environmental exposures. Consideration should be given to having the Coordinating Center provide GIS services or having cohorts with study teams with GIS experience. Also, the ongoing advances in genetic and epigenetic sequencing as well as descriptive work on the disease liabilities of specific variation in the human genome will necessitate consideration of at least some cohorts with genetic material and the expertise to capitalize on this.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

One possible existing resource is the Cystic Fibrosis Twin-Sibling Study (based at Johns Hopkins). It is a well characterized family-based study of 2086 individuals from across the United States with described and published environmental influences (such as climate, exercise, secondhand smoke, pets, etc.) as well as genomic data. The cohort data includes longitudinal outcomes such as growth parameters and serial lung function with ongoing data collection annually.

The additional IDeA States opportunity

Cohorts with subjects in variety of locations (urban, suburban, rural) would be better positioned to capture issues related to access of care; GIS analysis may be extremely helpful in this regard. Centers with existing cohorts could be partnered with IDeA centers to provide mentorship and research opportunities for post-doctoral fellows and junior faculty.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

While the use of existing cohorts with stored bio-specimens both decreases costs and speeds progress, there are some potential drawbacks. Existing specimen cohorts will likely not be optimal for the desired study goals, and will differ in specimen collection methods as well as targeted specimens. However,

using existing cohorts of specific target populations paired with state of the art specimen collection can provide optimal data for your stated goals. The Community Based Research Network (CBRN), originally funded by NIEHS, has successfully integrated and standardized data from electronic medical records (EMR) from five geographically dispersed community/migrant health centers (C/MHC). Women and children comprise a substantial proportion of this patient population including encounters for prenatal care. This joint effort of the National Center for Farmworker Health (NCFH), the Salud Health Centers (Colorado), the University of Texas Health Science Center, Texas A&M School of Public Health and Battelle has integrated community and academic institutional expertise to create this unique research network, which can be easily expandable to represent additional localities, including IDeA locations. Current locations are in Colorado, New York, Washington, California, and Michigan. NCFH has maintained relationships with community/migrant health centers across the US for 40 years, establishing the trust necessary for such collaboration.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

Clearly a need for shared protocols for specimen collection and laboratory analyses.

High impact areas of opportunity in addition to those listed

Farmworkers and their families as well as rural underserved populations.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

CBRN has had ongoing discussions with the Global Alliance for Preventing Prematurity and Stillbirth (GAPPS), part of Seattle Children's Hospital, regarding a collaboration which would entail the collection and storage of specimens from women attending the prenatal clinics at participating CBRN sites across the U.S. The GAPPS Repository is a standardized, widely-accessible collection of high-quality specimens linked to data from diverse populations of pregnant women. The repository supports research on normal and abnormal pregnancies, including how pregnancy affects maternal and child health after delivery, including fetal origins of disease and specimens are from women representing a range of racial/ethnic, regional, and socioeconomic backgrounds. Leveraging existing clinical data and resources from CBRN along with expertise from GAPPS would fit nicely within the stated goals of ECHO, and could be utilized to address the following outcomes among women attending C/MHCs across the United States: stillbirth, prematurity, fetal growth, injury, autism, and asthma. Further CBRN provides a unique opportunity for the longitudinal assessment of clinical outcomes among women and children attending C/MHCs.

The additional IDeA States opportunity

NCFH has contacts with community/migrant health centers across the United States, including those in

IDeA states, which would provide a prime opportunity to expand this unique data source into these underserved areas.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

[Respondent] wishes to note upfront our informed view, supported by Congress, that the follow-on to the NCS must include the integration of basic science. Furthermore, we believe NIH must offer resources to support shared core research infrastructure along the lines of what has been enacted into law via the National Pediatric Research Network Act (PL 113-55). As noted during a meeting with NIH leadership this past spring, the network is a very well-defined approach to support collaborative pediatric research, a model that would fit well within the proposed NCS follow-on orientation around thematic focus areas. We urge NIH to ensure basic science is integrated within the proposal and to include support for shared core research infrastructure. The coalition generally supports the use of existing cohorts to deploy scarce public resources wisely and to not attempt to duplicate existing data sources and biospecimen repositories. We also applaud the idea of standardizing data elements and asking standardized questions. Many of our institutions maintain or participate in cohorts and biobanks of a high quality, and we would urge and anticipate that NIH will closely scrutinize proposed cohorts to ensure quality, depth, size and other attributes are commensurate to achieve the study objectives being proposed. We also encourage NIH to be amendable to projects that propose add-ons to existing cohorts to capture additional data. Between now and the issuance of RFAs, we recommend that NIH inventory known existing cohorts that would likely be used as part of this follow-on project. Such an inventory would be useful to create a master list of cohorts that meet quality and other standards so the pediatric research community can fully understand what exists as well as what gaps or deficiencies may need to be addressed.

Additional core elements to be considered

As noted above, [Respondent] is adamant that the refocusing of the NCS provides a unique opportunity to achieve transformative gains to advance the health and well-being of our nation's children and that a significant element of this opportunity must include direct NIH support for basic research, including support for research infrastructure and for training of early-career investigators. Congress has recognized the larger imperative of providing such support for research infrastructure in recent years by enacting PL 113-55, the National Pediatric Research Network Act. In developing the vision for the revised NCS, we must recognize that much has changed in the more than 15 years since the NCS was originally conceived, particularly advances in science and research technologies and the emergence of new opportunities. One of our concerns with the original NCS was the lack of focus on and support for basic research to leverage the data collected. The refocused project presents an opportunity to intensify our understanding of human development and the impact of the environment writ large on said development and on the achievement of optimal health outcomes. But unless NIH actively supports basic research, the near-term will, we fear, be minimal at best. Related to this point, we strongly believe that support for basic research must include explicit resources to assist research institutions in attaining shared core research infrastructure that is necessary to conduct the research that will enhance our understanding of child health and development. Such cores – such as biomolecular core labs, bioinformatics platforms and cell imaging technologies – are increasingly cost-prohibitive for single institutions to obtain and often require the use of multiple aligned research teams and institutions to achieve their full utility. In addition to core infrastructure, we strongly urge that portions of awards be

dedicated to support training of early-career pediatric clinician/researchers.

Considerations for harmonizing data across cohorts

[Respondent] strongly supports data harmonization to the greatest extent possible to facilitate cross-cohort analytics. We recognize that leveraging existing cohorts may make this aim more challenging since data will likely exist in multiple formats. When this is the case, standardizing data retrospectively can result in sizeable costs of money and time. We would urge NIH to give careful thought to these considerations before embarking on a harmonization effort that is expensive and that may provide modest benefits in the end. In considering best practices to drive harmonization across cohorts, we would recommend exploring the PEDSnet model as one to emulate. The Pediatric Learning Health System is supported by PCORI and consists of eight participating children's hospitals located throughout the nation. PEDSnet sites operate existing networks in defined disease/condition areas, and the sites have collaborated to standardize data and research questions across participating institutions.

High impact areas of opportunity in addition to those listed

The project needs to recognize that the arc of development encompasses pre-conception through in-utero development, post-natal, childhood and adolescence and the influences of genetics and the environment on such development. We strongly encourage that NIH recognize the developmental origins of health and disease by ensuring adequate emphasis across the project. We also would encourage the NIH to consider establishing rare disease as a focus area given the more prevalent and common nature of the areas put forward in the RFI. Taking this action would recognize that children account for about 50 percent of the rare disease population and that 30 percent of these children die by the age of five. It would also acknowledge that these children consume a very substantial component of pediatric health resources. Given the challenges in conducting research on rare disease populations, particularly children, a focus on this issue via the follow-on project would be appropriate and would hopefully help advance understandings of environmental and related impacts on rare disease.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

Within the identified areas, we suggest an orientation around prevention that includes improving the health of populations through a focus on community involvement and better understanding the impacts of the environment in impacting upstream determinants of health. We also suggest: Asthma: The American Lung Association's Airways Clinical Research Centers is a model network for conducting large clinical trials dedicated to asthma treatment and often partner with NIH to co-fund innovative approaches to clinical research. Additionally, CMMI has funded a number of awardees focusing on asthma, such as the Nemours/Alfred I. duPont Hospital for Children's award focused on the use of a patient-centered medical home and community integrators and navigators. Additionally, Cincinnati Children's has a birth cohort of 762 allergic or asthmatic children with at least one parent who is skin-test positive for an aeroallergen. This data include exposure to traffic-related particulate matter at home, daycare, or babysitting sites determined by land use regression as well as phenotyping of household for mold, water, and dust analysis. Eosinophilic esophagitis: Cincinnati Children's possesses a

cohort of 896 children diagnosed with EoE. The majority have been genotyped for 5 million genetic variants. Detailed phenotypic information plus environmental exposure history exists through disease-specific and clinical research databases. This cohort offers the rare opportunity to study the diseased tissue in a pediatric cohort, with 4,000 endoscopic tissue biopsies available. Obesity: Existing patient and population dashboards should be explored that include risk stratification in the primary care setting. Additionally, CDC has funded a number of community-based obesity prevention interventions. Premature infants are at risk in several of these areas - The NHLBI PROP (Pediatric Respiratory Outcomes Program) is one cohort that would provide some maternal information, robust neonatal ICU information, especially regarding respiratory phenotype, and first year of life respiratory outcomes for babies born before 29 weeks.

The additional IDeA States opportunity

As leading pediatric research institutions and clinical trials sites, [Respondent] recognizes the sizeable challenge of recruiting patients from underserved regions of the country, particularly rural areas, and appreciates the RFI's interest in addressing this concern. It is our understanding that the NIH proposes to focus primarily on developing teams of clinical trialists within the IDeA network able to efficiently recruit pediatric candidates for clinical trials spanning all diseases and conditions. Furthermore, we understand that a project coordinating center would subsequently work with research institutions from any state interested in obtaining trial participants from IDeA sites to identify and recruit such patients. [Respondent] appreciates that NIH is contemplating providing support to educate and train clinical trialists and, as noted above, hopes to see such training extend into the larger project, particularly with a focus on training in research methodologies. We also appreciate the focus on IDeA populations but note that several non-IDeA states are home to sizeable rural and underserved populations that would address this need and that several institutions located in non-IDeA states have significant experience working with such populations. As such, we would encourage NIH to keep an open mind in designing the funding request as not to limit entirely to institutions in IDeA states but rather to provide a preference for proposals that collaborate with IDeA institutions. Finally, [Respondent] is pleased to see NIH recognize the value of networked research within the larger proposal and encourages NIH to consider opportunities, as noted above, to deploy a similar set of resources and approach to support the basic science component of the core NCS follow-on study.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Leveraging existing cohorts could have the benefit of lower costs. However, if those cohorts are largely clinic-based convenience samples, they will not adequately represent all the healthy and unhealthy profiles of America's children; nor will causal inferences necessarily be correct. Furthermore, clinic-based studies rarely integrate social, behavioral, and biological components well. It is important to have a multidisciplinary approach involving social scientists, epidemiologists, and obstetric and pediatric experts to have a robust data source that can address complex health problems. An inventory of such cohorts should be assembled and carefully evaluated before this approach is embraced. Having a nationally representative sample that can provide generalizable information about children provides the most benefit to address the needs of America's children by reflecting their status and the areas in which policy and development of health programs should focus. This is important not only for descriptive purposes, but for appropriate causal inference when conditional effects are a focus (e.g., gene-

environment interactions). There are various ways to obtain these samples and exploration should not be limited to what was attempted in the NCS Vanguard effort. By not giving the sample adequate attention, the science will be severely limited and the ability to reflect health disparities that may be reflected in the diversity (racial, geographic, access to health care, etc.) of the U.S. population may be lost.

Additional core elements to be considered

Collecting data during pregnancy is essential to get in utero environmental, social, behavioral, contextual, and medical exposures that are likely to be scientifically informative to children's life course. Relying on existing cohorts may jeopardize gathering information in this critical time period. If the cohorts are well constituted, they could yield subsequent pregnancies. However, this has the potential of excluding most first pregnancies, which may have unique characteristics – this is a weakness. Also, the core elements, as described, are not adequately specified. Chemical, physical, and psychosocial environments are correlated. It is critical that each of these environments be fully and appropriately measured so that the true causal influences can be properly studied. Drawing in a broad disciplinary community that has expertise in collecting and analyzing these measures is essential to having this study reach its scientific potential.

Considerations for harmonizing data across cohorts

An examination of perinatal and pediatric cohorts (active or no longer recruiting) could also yield information about the complexities of harmonizing data that have already been collected. There have been efforts to harmonize data across existing cohorts that can provide insights. An example is an analysis funded by the Centers for Disease Control and Prevention that brought together three perinatal cohorts – the PIN Study (UNC, PI Anna Maria Siega-Riz), the Omega Study (U Washington, PI Michelle Williams), and the POUCH Study (Michigan State U, PI Claudia Holzman). Each of these studies collected extensive survey and biologic data during the perinatal period, however, when the collaborative team sought to create a common analysis dataset, the number of comparable variables was limited, in some cases because of the timing during pregnancy when data were collected. The analysis was successful (see: Luque-Fernandez MA, Gelaye B, Vander Weele T, Ferre C, Siega-Riz AM, Holzman C, Enquobahrie DA, Dole N, Williams MA. Seasonal variation of 25-Hydroxyvitamin-D among non-Hispanic black and white pregnant women from three U.S. pregnancy cohorts. *Paediatric and Perinatal Epidemiology*, 2014;28:166-76, PMC3946392), however, not as robust as a study that has common protocols for data collection. Existing cohorts, including those that are no longer collecting data, could be used to test this approach before investing in extant cohorts as the ECHO cohorts. The NIEHS-funded CHEAR project may be able to address some of these issues to inform ECHO. If there are plans for new data collection, the PhenX Toolkit should be consulted for measures to include. The PhenX Toolkit measures are well established high-quality, low-burden measures intended for use in biomedical, epidemiological, and genomic research (see: www.phenxtoolkit.org/).

High impact areas of opportunity in addition to those listed

Collecting survey, biologic, and environmental data at multiple points during the prenatal period, rather than relying on surveys that gather retrospective information and medical charts that might reflect biological states during pregnancy is essential to understand the early life origins of health and disease. Recall biases are well known when a parent has a sick child and such biases can lead to incorrect conclusions and ultimately inappropriate policies.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

A centralized approach that brings together the best interdisciplinary researchers across the U.S. could yield new strategies to address data collection and analytic methodologies. The use of existing cohorts may not produce the scientific teams that can push the science forward. For instance, both IOM panels that reviewed the NCS were chaired by social demographers, and yet this perspective was never really incorporated in NCS leadership within NICHD and only partially among the PIs of the original study.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

We support the expansion of research opportunities across the US as identified in the IDeA states network. Our concern is that these states alone are not necessarily going to reflect the diversity of populations across the country, or even the rural and medically underserved populations which are the target of the IDeA program. We recommend that the goals of the ECHO program be clearly articulated and that metrics and measures of success be identified, monitored, and reported yearly.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

[Respondent] supports the application of personal exposure monitors to characterize exposure levels and patterns for correlation with acute and chronic health effects. However, previous personal exposure instruments can be burdensome thereby increasing the frequency and duration of time when the monitor is not worn according to protocol. These periods contribute to exposure misclassification bias, defined as times when exposure data are not representative of exposure. RTI's MicroPEM™ technology (NIEHS Grant U01ES016093) provides particulate matter (PM) exposure data at the personal level in a

low-burden package that can be worn by children to significantly enhance respiratory health research studies. The MicroPEM provides fully representative personal exposure characterization by simultaneously defining the integrated exposure as filter based measurement as well as the patterns of exposure in real-time in a wearable low burden package weighing less than 240 grams. Collection of either PM2.5 or PM10 relate the collected data to targeted respiratory system deposition zones, allowing health-based associations to be studied against disease outcomes. On board collection of quality control data and accelerometer motion allows straightforward validation of wearing compliance and enables estimates of respiratory ventilation rate and potential dose. RTI has used the MicroPEM in children's health studies, including Children's Health After the Storms (CDC Contract #00HCUGC-2010-87205) and the Children's Environmental Health Center investigation of asthmatic children's longitudinal environmental exposures (NIEHS P01 ES-018181; EPA STAR GAD #834515010). Recently, the MicroPEM is being used for exposure studies for pregnant women cohorts, including B-WELL-Mom in the US (NICHD Contract #HHSN275201300026I - HHSN27500005) and SEPAGES in France. The ECHO Program may have an opportunity to leverage the current use of this technology in existing cohorts and to add use in other established cohorts to understand the relationship between PM exposure and asthma severity in children at various developmental stages.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

See response to 'anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies' for a potential resource consideration.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Data from extant cohort studies must be compatible to achieve the goals of ECHO as defined. When possible existing cohorts can be leveraged by harmonizing the data. This compatibility is largely two-fold: first, data terminology must be harmonized to effectively combine data for the purpose of meaningful analysis with sufficient power and sample size; second, the technology through which data is collected, and the form in which it is captured, must be compatible to effectively and efficiently combine data from existing cohorts. Collection of harmonized and standardized data elements is critical to support data exchange and interoperability among data resources. Potential benefits include integrated and more coherent data processing mechanisms, semantic standards support more efficient maintenance and sustainable data management, as well as facilitate more immediate insight and knowledge discovery from analyses of primary and secondary data stores. Data sets generated by independent and often siloed systems may have a variation in how things are named. Names and meanings are often not chosen from standardized vocabularies and therefore, can vary across studies. To ensure that data can be shared broadly and optimally used across research, it is important that variable names, survey questions or metadata be described in a standardized way. Use of common data

elements would help to maximize the value and interoperability in advancing research. A current major drawback, there is no unified semantic framework for integrating terminology efforts across clinical research disciplines and there is a lack of specific pediatric focused standardized data elements, which can be shared across studies. These standards are requirements which are intended to establish a common understanding of the meaning or semantics of the data, ensuring correct and proper use and interpretation of the data by its owners and users.

Additional core elements to be considered

Additional core elements include: the use of heterogeneous data from diverse sources; and the design of semantic models to provide flexible and meaningful integration and discovery of heterogeneous data from large data collections and its enrichment from external semantic web resources. The foundation of clinical and biomedical research is shifting increasingly toward a collaborative data-driven paradigm. Benefits gained from combining and mining large, distributed or heterogeneous datasets are dislocating the traditional model of autonomous research. More and more contemporary studies draw upon critical primary and secondary, heterogeneous data from diverse sources to improve knowledge discovery and facilitate decision support. Increasingly, the demands of modern research strain current systems to answer complex questions that mine heterogeneous data in large or distributed sets. As a result, demand continues for improved, scalable tools that effectively exchange, integrate and analyze heterogeneous data to uncover real insight from the existing and emerging data landscape. Contemporary systems efficiently store data, copy data between locations and execute tasks, but essentially preclude direct access to the meaning/significance of information. Although new tools can improve the workflow of SQL systems in assorted ways, they often do not address the fundamental limits of relational databases (RDBs) that hinder exchange, integration and analysis datasets. To achieve meaningful integration and exchange of data and to reach more comprehensive insight from the growing data supply, digital systems require next generation technologies such as Semantic Web Technologies (SWT). Semantic technologies employ schemas/resources that enable computation based on the meaning of information and linkage between data elements. As a suite of open source standards – established by the World Wide Web Consortium² – SWT enable data computation via explicit and interoperable machine-readable linkages among entities. Machine-readable linkages within and across models provide semantic description and integration of data content.

Considerations for harmonizing data across cohorts

Child health outcomes are intrinsically multidimensional, and so are their exposures to environmental risks. This poses a tremendous challenge for the government to accurately identify the dimensions of those risks and track their influences on health outcomes. This source of inaccuracy or misclassification is exacerbated by different survey modes or samples and can bias our understanding of exposures and health outcomes across time. To harmonize NIH data with minimal exposure and outcome misclassification and more accurately and effectively track their longitudinally dynamic interrelationships, a 2-stage design may be necessary. First, for maximum flexibility and precision of harmonizing numerous measures among children of varying ages it is important to maintain a calibrated item pool through Item Response Theory (IRT) (Irwin, et al, 2009) that harmonizes outcome measures of the same construct across different samples or cohorts. This allows statistical Linking (Ogasawara, 2001) between child and adult item pools, opening opportunities to predict effects of environmental influences (e.g., pollution, behaviors, and genomics) on children's health and disease development now and into adulthood. To optimize this calibrated item pool, Booz Allen possesses expert IRT methods, such as augmentation methods for subscale scores, Differential Item Functioning (DIF) capabilities, and methods for equating (Hanson & Beguin, 2002) person propensity scores to rate outcomes and thus eliminate effects of survey modes on responses to make a fair comparison of individuals. Second, since

accurate dimensions of environmental exposure and health outcomes have been identified in the first stage of item calibration, it is possible to harmonize these data in longitudinal multi-trait-multi-method models. This approach not only tracks the dynamic inter-relationship between the environment and health at repeated points in time, but it also provides errors-in-variables diagnostics to refine which adjusted covariates are included in data harmonization propensity matching processes.

High impact areas of opportunity in addition to those listed

The variety of data collection methods available for ECHO will continue to grow with the evolution of new technologies—new sensors, new patient-generated data capabilities and a rapidly expanding suite of exposomic technologies, including genomics, metabolomics, adductomics, proteomics, transcriptomics, etc. Through federal programs including the VA’s Million Vet Program and the DoD-VA Individual Longitudinal Exposure Record (ILER) along with the interagency Exposure Science in the 21st Century, efforts are underway to develop and leverage new exposure assessment technologies and approaches for assessing individual exposures. These advances must be considered in ECHO’s study design, data collection, and data harmonization efforts. For example, in 2020, new –omics (genomics, metabolomics, proteomics, transcriptomics, etc.) techniques may be ready to use to enhance the ability of NIEHS to assess individual exposure to VOCs or PM2.5 that were not possible in 2015. To capitalize on these rapidly evolving individual exposure assessment technologies, the tremendous amount of raw data and metadata available for analysis, as well as the expanded exposure data available from these new technologies, it will be critically important for NIEHS to:

- Implement strong data collection version control and data documentation for meaningful data analysis over time.
- Ensure a standard suite of biospecimens are collected, archived, and preserved at the appropriate stages of development across all studies funded under ECHO.
- Establish an identifiable, central, and harmonized repository for all study data collected under ECHO that permits “newly discovered” individual exposure data to be added to the participants’ ILER and exposome at the time it is available.. Doing so will enable NIEHS and ECHO researchers to reduce exposure misclassification, permit enhanced exposure stratification in the studies funded and increase the volume of exposure data available for analyses allowing an increased number of research questions to be answered retrospectively and prospectively.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

Standard methods of data collection relying largely on in-person interaction are cost prohibitive and inefficient, while mobile health technologies and web-based data collection methods are growing in efficiency. A hybrid suite of data collection methods and modes provides the most sound approach, while addressing the generational and socioeconomic disparity of technology use associated with a heavy use of one mode over another (e.g., mobile application, direct mail, web-based platforms, in-person interaction, etc.). To address the rapid pace of current and potential advances in biomedical research, data science, analytics and technology, development of data collection and analytic systems or tools under ECHO should be flexible, scalable, expandable and modular. When implementing such tools, certain key design considerations should be followed, including a:

- Flexible and scalable architecture and data model whereby new functionality and/or enhancements to existing functionality can be implemented without extensive system redesign and allow for seamless integration of new data types and expansion of data volume
- Semantic web-based “Linked Data” metadata model that facilitates contextual organization of descriptive metadata and data files, which enable users to find, examine and analyze related content and also allow establishing associations internally and with external data sources for advanced data visualization and analytics
- Modular approach to data and metadata storage that enable easy replacement with more advanced state of the art technology solutions (e.g., tools for big data or graphical database for metadata representation)
- Dynamic data-driven user interface so

changes to system content will be automatically reflected in the user interface and will not require software version releases, saving time and cost The integration of data science and information technology is fundamental to establishing a data collection and analytic suite that reduces costs, improves efficiency and derives new insights from ECHO community efforts.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)
(*Submitter left answer blank*)

The additional IDeA States opportunity

(*Submitter left answer blank*)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

While there is clearly some efficiency in leveraging existing cohorts for investigating environmental exposures for some pediatric health and developmental outcomes, I don't see how one could truly investigate important and novel hypothesis related to pre- or perinatal environmental exposures, especial fetal exposures, in relation to subsequent health and developmental outcomes using existing cohorts. You need to pose the question, ensure you have the right measures of exposures and outcomes and then collect the data. If you don't measure the environmental exposures at the right time with sufficient precision you won't understand the causal mechanisms underpinning the exposures-diseases of interest, nor will you be able to identify preventive measures for public health policy and practice. This concern exists across all the focal areas identified in the RFI.

Additional core elements to be considered

(*Submitter left answer blank*)

Considerations for harmonizing data across cohorts

Harmonizing data across cohorts sounds good in theory but only makes sense with new cohort studies. I question the feasibility and cost efficiency of imposing it on existing studies.

High impact areas of opportunity in addition to those listed

(*Submitter left answer blank*)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(*Submitter left answer blank*)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major

health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

ECHO raises challenges of data and metadata creation, organization, manipulation and analysis that are of unprecedented complexity and intricacy. Progress on these challenges requires dedicated resources, but can also leverage other NIH initiatives such as BD2K. At early stages of the data-to-information/insight-to-knowledge/action chain, data provenance, versioning and integration will be central. Later on, even under optimistic scenarios, data harmonization will demand powerful, automatic methods for editing and (multiple imputation). Combining data from extant cohorts formed in multiple ways necessitates characterizing their individual and collective representativeness. Scientific generalizability to the population(s) level needs both base weights (to reduce bias) and replicate weights (to estimate variability). New methods for principled curation of the data will help ensure reproducibility of ECHO research. The “usual” issues of privacy and confidentiality will be exacerbated by there being not only personally identifiable information, but also institutionally identifiable information. Resolving these issues will allow cohort-level inference as well as population-level and individual-level inference, the latter using modern methods for predictive analytics. Two overarching themes are data quality (DQ)—not only accuracy but also accessibility, completeness, relevance and timeliness—and uncertainty quantification (UQ). The entire ECHO effort will be deeply informed by approaches such as the total survey error/total survey quality paradigms, whose development has been led by RTI researchers, which are now being translated and extended to other contexts. UQ is likewise critical, especially given the diversity of ECHO data. Organizations such as RTI International, with broad capabilities that span data collection, curation and analysis, and with deep, multi-faceted understanding of both DQ and UQ, are poised to make major contributions to ECHO.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

Throughout the decades of my research on environmental exposures and children's health, I have constantly encountered a significant barrier to integrating state-of-the-art data collection and that is the important interface with healthcare providers and healthcare facilities. I would love to see NIH invest in research to incentivize healthcare providers to collaborate in these very important cohort studies. The major issue is the time constraints of clinicians and confidentiality issues that make it difficult to place research project personnel in clinical areas. For example, nothing could be more important for science than the collection of cord bloods or placental samples in pregnancy cohorts. However the resources that are needed to convince multiple clinical agencies (few cohorts deliver in one system with one provider) to cooperate in collecting these samples often exceed the capacity of a budget of an R01. Even if the subject has consented to give a cord blood, the resources needed to assure that it is collected is formidable. A significant advancement would be to provide funding for biobanks of these samples on all consenting pregnant women in the institution, so that investigators need only to access the tissue of their cohorts and not have to incorporate the costs of obtaining the samples in their protocols. It's just unforgivable that this rich source of information on maternal and infant physiology is just discarded because of the lack of resources to coordinate data collection across multiple institutions and care providers. Collection/storage of these samples across clinical settings, would be a significant contribution to advancing science in this area.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Potential benefits include: 1) reduced cost and 2) reduced participant burden. Potential drawbacks include: 1) exposure data might be limited to only a few domains and 2) outcome data might be limited to only a few domains and 3) exposure data might be representative of current exposure levels.

Additional core elements to be considered

Exposures - Measures of psychosocial stress. Outcomes - renal and cardiovascular outcomes.

Considerations for harmonizing data across cohorts

My research experience is limited to brain outcomes. For early outcomes, a standardized neurological examination for infants was developed in the NINDS-sponsored ELGAN Study. This could be used as a standard data element for studies of neurological outcomes. The Bayley Scales of Infant and Toddler Development can serve as a standardized approach to assessment of early cognitive functioning. At older ages the NINDS toolkit could be used to harmonize across studies.

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Extremely Low Gestational Age Newborn (ELGAN) Study was designed in the late 1990s to evaluate the hypothesis that perinatal inflammation increases the risk of brain disorders in human neonates born extremely premature. The study enrolled 1500 extremely low gestational age newborns (ELGANs) born at one of 14 U.S. hospitals over a 28-month interval. 1206 survived to 24 month adjusted age, and 896 of these children have been evaluated at 24 months of age and 10 years of age for developmental and health outcomes, with an emphasis on neurological disorders, including cerebral palsy, acquired microcephaly, seizures, autism spectrum disorders, intellectual deficit, and attention deficit

hyperactivity disorder. We have collected anthropometric data at birth, 28 postnatal days, 36 weeks post-menstrual age, 1 year adjusted age, 2 years adjusted age, and 10 years of age. Microbiological and histological evaluations have been completed on placenta specimens from study participants and levels of 25 inflammation-related proteins have been measured in blood samples collected from participants on postnatal days 1,7,14, 21, and 28. Neonatal brain ultrasound images have been evaluated on all study participants and brain MRI images have been collected at 10 years of age on a subset of 187 participants. In addition, we have stored specimens of placenta, umbilical cord and neonatal blood from ELGAN participants. From archived specimens of placenta we have extracted DNA, which could be used for epigenetic studies and RNA, which could be used for gene expression studies. In addition, we have set aside samples that can be used for measurement of environment metals.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

On behalf of ... I see many potential high-impact benefits emerging from the collaboration across existing cohort studies to explore the effects of environmental exposures occurring during gestation, infancy and childhood. Most significantly, the incorporation of exposure data across different domains would allow researchers to better characterize the “exposome”, which encompasses the totality of human exposures that include the chemical, social, physical, environmental, epigenetic and psychological domains, all of which contribute to health and illness in childhood and ultimately adulthood. By combining these data from multiple cohorts, data collection and analysis across cohorts could benefit one another, creating larger datasets with more complete exposure profiles and increased statistical power. Such a centralized data warehouse would enable the study of multiple exposures, both within each domain (e.g. multiple chemicals) and across domains, such as the interrelationship between chemical exposures and psychosocial stress. The field of environmental health is currently developing the statistical and theoretical tools to approach such mixture problems, and a central repository of data would go a long way towards advancing knowledge, tools and methodologies on the effects of mixtures of exposures. However, a number of potential challenges should be considered. There are logistical difficulties associated with integrating data from multiple extant cohorts. These data sources will be drawn from different communities with unique cultural expectations and experiences, and with different environmental exposures and challenges. Researchers from different cohort studies may be hesitant to combine their data or alter their data collection methods to align with the larger purpose of the large-scale study. From the outset, it would be important to articulate a clear and transparent data sharing and authorization plan that will be agreeable for all PIs.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

Harmonizing data across diverse cohorts will be critical for the success of this project; my previous multi-site interdisciplinary environmental health research experience has taught me that this stage of the research process requires advance planning and high levels of patience and cooperation across

stakeholders. Data collected in different cohorts will most likely be maintained using customized hardware and software, management plans and data formats, all of which may hinder or delay data analysis on fundamental questions about children's health and environmental exposures. The quality of the data (reliability, validity, quality assurance) will mostly likely also be diverse across cohorts and within cohorts, depending on the source of the data. In addition, it is likely that data collection methods may have changed or evolved over time even within a single cohort. A high level of commitment and cooperation from each participating cohort would be essential to the success of this part of the project. Additional resources and/or funding may need to be allocated to universalize the data collected, stored and analyzed in each cohort.

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

Big datasets are increasingly being used to address environmental health questions due to improved data collection methods, data storage innovations, greater computational capabilities, and electronic medical record collection. The ECHO proposal has enormous potential to create one of the largest environmental health databases yet, with which innovative analytical techniques could be applied such as k-means clustering, principle component analysis, GIS-mapping and more. To maximize the use of ECHO data for Big Data studies, it would be critical to involve leaders with experience with Big Data research across disciplines (engineering, computer science, health informatics, even climate science and more) early in the process to ensure key capabilities for Big Data analysis are built into the data collection, storage and access systems. Finally, issues of privacy and confidentiality of the data may be a concern for participants and administrators once data is shared across cohorts.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

While a set of standardized data elements will be useful, a diversity of cohorts and measures should be considered. More will be learned by funding many different cohorts that represent populations with a variety of geographical, age, gender, racial/ethnic and socioeconomic characteristics. Cohorts should sample from the entire span of childhood and not just early life exposures which tend to account for only limited variability in outcomes. Finally, dependence on observational studies will have some of the same major drawbacks as the original NCS -- limited to hypothesis generation and unable to infer

causality or directly inform policy and practice. Substantial evidence and hypotheses are already available about the potential adverse or beneficial effects of many exposures on child health, well-being and development. Therefore, it would be wise to devote some funds to solution-oriented experimental research testing the benefits of manipulating those exposures in real world settings.

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

Harmonizing data should not harm the quality or integrity of any individual study. Maintaining the quality and integrity of each study should be prioritized. The assumption that one can simply combine data across heterogeneous studies simply because they use the same measures ignores many threats to validity and often leads to spurious results. Just because the software and mathematics are available to do so does not make it appropriate to do so. Instead, it should be considered exploratory.

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Childhood Obesity Prevention and Treatment Research (COPTR) Consortium funded by NHLBI and NICHD is currently conducting four different randomized controlled trials using common measures to test different interventions. Vanderbilt University (PI, Shari Barkin, N=610) and University of Minnesota (PIs Simone French and Nancy Sherwood, N=534) are conducting prevention trials with normal weight pre-school children and their families, Stanford (PI Thomas Robinson, N=241) and Case Western Reserve (PIs Elaine Borawski and Shirley Moore, N=360) are conducting secondary prevention/treatment trials with 7-11 year old and 11-14 year old overweight and obese children, respectively. A Research Coordinating Unit at University of North Carolina (PI June Stevens) also manages a database of common measures collected in all four studies. Each study is 3 years in length, contains a vast majority of racial/ethnic minority and low-income families (children and parents), and collects annual (four time points) anthropometry (height, weight, waist, skinfolds), 4-7 days of 24-hour accelerometry to objectively assess physical activity, sedentary behavior and sleep, 3 x 24-hour dietary recalls using NDS-R, blood pressure (Stanford and Case), and parent/self-reported behavioral, psychological, social, environmental and demographic measures according to a common protocol. In addition, Stanford and Case Western Reserve have fasting blood and Stanford and Vanderbilt have saliva biobanked samples suitable for studying genomics, epigenetics, metabolic markers and environmental exposures at baseline and/or over time. Retention in all four studies is extremely high ranging from 90.3% to 98.8% after one year and, to date, following a similar pattern after two years. Three-year follow-up is now starting. All four studies are also preparing to continue follow-up beyond three years, depending upon available funding. As a result, the COPTR Consortium of four studies with very well-characterized samples would be appropriate candidates to help address two or three of the four identified focus areas with further

follow-up.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

[Respondent] would like to suggest sampling for a study of child health by using the children of a nationally representative study such as was done with the Children of the NLSY79. We suggest two possibilities. We could use a combination of children born to sample members in the NLSY79 and children born to sample members in the Children of the NLSY79. A second possibility is to support the start of a new NLSY cohort and follow the children of this group as they are born. We would know the sampling properties of these samples so we could project to something approximating national numbers. The advantage of both of these approaches is that we could know a great deal about the mothers and would be able to do pre-natal testing. The disadvantage would be that it would take several years to achieve the complete sample and the sample size would be smaller than envisioned in the original NCS (probably on the order of 5000 in the first approach and 10,000 in the second.)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

Climate change is the most important environmental health problem confronting society. We believe that some of the funds from the ECHO program should be used to support research related to the impact of climate change on children's health. Children are particularly vulnerable to some of the exposures that are projected to increase in a changing climate such as extreme heat. Additionally, extreme heat has been shown to induce preterm labor through dehydration, which is a particularly important health concern. In my previous research, colleagues and I also found decreased birthweight for babies that gestated during large wildfires and in current research on wildfire smoke exposure, another exposure that will increase in a changing climate, we have found that asthma hospitalizations and emergency department visits are significantly higher. Climate change is also projected to increase pollen and mold spore counts which can exacerbate asthma. More research is needed into an understanding of other extreme weather events such as droughts and flooding and their health impacts on children at all life stages. Important health outcomes for children during these events could be depression and mental health, nutrition, and infections. Additionally, there is a need to evaluate the health impacts of local, regional, and national climate change policies on children's health, particularly taking into account equity across populations. Much of this research could be undertaken using existing or newly developed cohorts.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

Climate change is the most important environmental health problem confronting society. We believe that some of the funds from the ECHO program should be used to support research related to the impact of climate change on children's health. Children are particularly vulnerable to some of the exposures that are projected to increase in a changing climate such as extreme heat. Additionally, extreme heat has been shown to induce preterm labor through dehydration, which is a particularly important health concern. In my previous research, colleagues and I also found decreased birthweight for babies that gestated during large wildfires and in current research on wildfire smoke exposure, another exposure that will increase in a changing climate, we have found that asthma hospitalizations and emergency department visits are significantly higher. Climate change is also projected to increase pollen and mold spore counts which can exacerbate asthma. More research is needed into an understanding of other extreme weather events such as droughts and flooding and their health impacts on children at all life stages. Important health outcomes for children during these events could be depression and mental health, nutrition, and infections. Additionally, there is a need to evaluate the health impacts of local, regional, and national climate change policies on children's health, particularly taking into account equity across populations. Much of this research could be undertaken using existing or newly developed cohorts.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

While opportunities to leverage existing pre-conception or conception research cohorts to collect new standardized data elements exists, the generalizability and the type of information collected previously from these cohorts will vary. While cost effective to use existing cohorts, the way in which existing data have been collected across these studies will likely vary considerably and the generalizability will be dependent upon the population from which they were selected as well as the participation rate. If existing cohorts are leveraged, the investigators that developed those cohorts should be "at the table" and included in the design and implementation of any future studies. Most researchers do not want to invest years of time and effort gathering data for studies without the ability to use these data to further the science in their fields of interest.

Additional core elements to be considered

Maternal age, weight (pre-pregnancy), weight gain during pregnancy, race and ethnicity, paternal race and ethnicity, intendedness of pregnancy, depression, exposure to violence, exposure to drugs (illegal and Rx), intake of other supplements during pregnancy. Infant feeding practices

Considerations for harmonizing data across cohorts

This will be challenging. If existing cohorts are used, only new data collection can be done in a similar manner whereas existing data will need to be mapped and determine if core elements, if measured, were assessed in the same way. Given that the existing cohorts will vary considerably as will the capacity to follow them up and collect additional data, results may be somewhat fragmented and common data elements may be limited. Something else to consider is using information from electronic health records. The Health Care Systems Research Network (formerly the HMO Research Network) has spent many years and considerable resources to harmonize data elements across multiple health plans and health systems. There are many lessons to be learned from these experiences.

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

It would be cost effective to recruit women early in pregnancy in settings where health care information is available for the peri-conceptual period. The number of commercially, privately, and federally

insured women who receive care in managed care organizations has increased. Information from the electronic health record and other health care and administrative databases from Kaiser Permanente have been leveraged to study topics related to maternal diabetes and obesity and childhood health outcomes including those listed in the focus areas. Scientists in multiple regions of this health plan, particularly from the Southern and Northern California regions, have demonstrated expertise in studying many health topics using information collected during routine health care visits supplemented with additional information gathered specifically for research. Facilities for processing and storing new biospecimens are available and research lab orders can be placed using the electronic health record. Due to the deployment of the electronic health care record in various settings, data could be collected from other health care settings in a similar manner. However, the benefit of launching studies in a managed care setting is that information from pharmacy, laboratories, and inpatient and outpatient encounters can all be linked, whereas information from fee-for-service systems may only provide a snapshot of care at various points in time and not a long term record of different types of health care (and mental health care) encounters for individuals who go to different facilities in and out of their network for different types of care.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

An existing study that has information starting from the 2nd trimester of pregnancy is the HAPO Follow-Up study (www.hapo.northwestern.edu, Boyd Metzger, PI). Currently recruiting mothers and their offspring 9-15 years old from 10 centers (4 from North American, 3 from the US) through 9/30/16, funds could be used to conduct additional analyses on biological samples and to conduct future follow-up visits or other forms of data collection. Additional information on this study, funded by the NIDDK, is readily available. If studies that do not presently have pregnancy data are considered, the SEARCH for Diabetes in Youth (www.searchfordiabetes.org) has been studying youth with type 1, type 2 and other forms of diabetes diagnosed before age 20 years since 2000 drawn from five centers in the US, with repeated measures for some core elements. With an additional five years of data collection planned with funding anticipated from the NIDDK and CDC (pending notices of award), applications could be generated for ancillary studies to address many additional research questions. This is a highly motivated group of researchers that have worked together for 15 years.

The additional IDeA States opportunity

This is unclear to me. The IDeA States are not referenced in the materials provided. Does this refer to the "Individuals with Disabilities Education Act" or something else?

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Leveraging existing cohorts implies that what happened years ago is relevant today yet this is not necessarily so. If one examines prenatal vitamin mineral supplement use over the last 30 years, supplement doses and components have changed dramatically without evidence-based data to support the benefit to the pregnant woman and fetus. Further macro and micro nutrient intakes and the food

supply are constantly changing with potential effects on the growing child. Existing cohorts have not collected data on vitamin mineral supplementation brand, dose and frequency of intake and data on diet across trimesters of pregnancy to address the role of nutrition in the newborn and young child. Thus while existing cohorts can provide historical context to capture rates of pregnancy complications and outcomes, nutritional status has not been adequately assessed nor relevant to today's pregnant woman and the newborn. Importantly rising rates of prepregnancy and childhood obesity have implications for a shorter life expectancy in recent compared to older birth cohorts. Given the importance of metabolic health across the life course, it is imperative to develop new prospective cohort studies of women early in pregnancy through the offspring's first year to identify windows of exposures that lead to vulnerable pregnancies and adverse child health. A recent issue of Reproductive Toxicology focused on the role of environmental exposures on health across the life course, where it was crystal clear that the challenges of today's environment from water, soil and air, on health require an assessment of current exposures in utero. To attempt to capture these data retrospectively by recall or from available biospecimen will lead to biases in detection of environmental exposures and in health effects that would severely limit the ability to formulate policy in pregnancy when the twofer is the optimal prevention modality to address intergenerational health.

Additional core elements to be considered

Several key environmental exposures in pregnancy and early life are essential to the understanding of health across the life course. Today many women return to work soon after delivery and therefore breast feed exclusively for a brief period followed by a rapid transition to breast and bottle feeding. It is key to understand the extent of breast feeding and the contents of the bottle among women who both breast and bottle feed as well as examine the role of infant diet on health because women are now feeding expressed breast milk in the bottle to the infant. The health consequences of these types of infant feeding are not well known especially among diverse ethnic groups and the disadvantaged. Further consideration of the role of weaning foods and age at introduction of solids has not been addressed yet we are aware that potential exposures at specific developmental stages are key to link environmental exposures to health. A carefully designed and administered questionnaire is essential for these data collection. While our country has focused on obesity as a major health condition, we fail to recognize the need to understand the role of linear growth in child health. It is important to consider that collection of anthropometric data i.e. weight and height need to be measured repeatedly in recognized intervals relevant to overall development and in a standardized manner to be able to derive meaningful growth data in a longitudinal study. Biological samples should include blood and buccal cells for assessment of epigenetic profiles and linked to examine environmental exposures e.g. diet that modifies the epigenome. Pediatric cancers are on the rise without adequate risk factors to address prevention. Focus on specific pediatric cancers such as acute lymphoblastic leukemia should be considered given the life-long adverse consequences among pediatric cancer survivors.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

1. The NCS failed largely because it ignored the extensive experience in the recruitment, enrollment and follow up of pregnant women that exists in the US academic community and even in NICHD! Carefully

validated pregnancy protocol is essential and within the cost range of many large studies funded by NIH. A very large sample could be enrolled using the funds allocated by congress. 2. It is critically important that the sample be a truly representative sample, which can only be obtained by some form of probability sampling. No major survey in the US obtains its sample through convenience sampling, and to rely on convenience samples for a major study such as NCS-A would be scientifically disastrous. 3. There is a temptation to think that new technologies in monitoring or data analysis can replace considerations such as the above. But such technologies, do not replace but can only supplement sound hypothesis formulation, study design, population sampling, recruitment, sample maintenance, and data analysis that takes account of potential bias and confounding.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Numerous studies using multimodal neuroimaging including structural MRI, functional activation MRI and DTI to better understand factors that influence the wide variability in brain structure and function among individuals of similar ages. The questioned is, why some individuals perform very well on cognitive tests, school performance, and behavioral competence, and, why some children perform more poorly within the developmental environment? My collaborators and I have shown that pubertal hormones predict more variability in brain structure and function than chronological age, that variability in measures of cognitive function are related to changes in brain structure over time, and most importantly, that children and adolescents from lower socioeconomic status have smaller cortical surface area than children from wealthier families. We have long known that poverty has negative consequences on cognitive tests and school performance, but, what we need to investigate are what resources and environments are afforded the more affluent that could be ameliorated in our poorest children from conception to adulthood. One drawback of existing cohorts is that some of the most important questions in the field of developmental cognitive neuroscience have only been recognized after recruitment and study of the children. These can be very time sensitive, and you can't go back in time to answer these questions. For example, in the PING study, we did not collect information on pubertal status. As described above, this is a critical element to beginning to understand what tips the balance on risk and resiliency for developing neuropsychiatric disorders, drug abuse, etc. Again, this is just an example, but, similar examples can be considered moving forward. We have not measured more detailed assessments of the family/developmental environment (i.e., exposure to pollutants, nutrition, health care, child care, etc.). New cohorts would be needed, I think, to address these very important questions.

Additional core elements to be considered

I think the goal of all of us in developmental cognitive neurosciences is to understand how the brain develops to achieve competence in health and society, and what factors contribute to those who do well, vs. those who have problems of any kind. Understanding the variability around the age-mean of brain or cognition might help determine "interventions" that could improve the lives of children below the age-mean on any variable of interest. It is important to note that understanding variability around the mean should be thought of independent of whether the subject is typically developing (poor or wealthy?) or, have neurodevelopmental disorders spanning the range (i.e., phenotypes on target cognition and behaviors rather than diagnosis-specific).

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

With respect to the impact of heavy prenatal exposure to alcohol, better diagnosis is one objective, integrating multiple forms of data. Knowing what is affected and WHEN is key because the brain develops within the environment. The brain changes differently over time long after the in utero environment. How do we predict the variability around the mean? Genes? Environment? Individual differences, and factors that predict better adaptation are important. Understanding change in the brain and cognition over time during development, and how that relates to facial morphology from combined face brain analyses. Can we use facial data earlier in development to predict later brain and cognitive development, in hopes of earlier intervention for children who will have problems later in development? We should capitalize on neurocognitive measures, in the briefest battery possible (with may be different depending on the age of participants), assess change over time on these measures along with changes over time in the brain. The ultimate goal should be to understand environmental (SES, nutrition, family stress, educational environments, exposure to adversity, any interventions of any kind) to help understand inter-individual variability. If we could do that, we could work towards changes in the environment (most likely interventions of some sort, behavioral, cognitive, etc.) to improve adaptation of those most negatively affected.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Collaborative Initiative on Fetal Alcohol Spectrum Disorders has a large cohort of children with and without heavy prenatal alcohol exposure. We have collected brain imaging data at multiple time points at various national and international sites over the last 5 years. We have brain imaging data on well over 250 participants in this study, and continue to follow these participants. Another very important birth cohort of 6,000 children have been identified in the PASS study. The prevalence of FASDs in the wine producing Cape Town region of South Africa (SA) is astronomical relative to other regions, likely because socioeconomic disadvantage and historical practices of paying farm laborers with wine have lead to the cultural practice of socially acceptable heavy weekend binge drinking. Given this history, and unlike other places in the world where stigma is associated with drinking during pregnancy, women in this

population are quite candid about their drinking patterns. There is still debate in the popular press among women in the US and other Western countries as to whether “moderate” drinking risks the health of their unborn fetus [3]. Most human studies on the impact of prenatal alcohol exposure on brain and cognitive development utilize retrospective samples and rely on mothers’ recollection of alcohol consumption patterns years prior to study recruitment (and, likely under-report given stigma) [4], and/or select prospective samples of children with “heavy” exposure vs. low or no exposure, without the complete range of drinking patterns within the population of study (e.g., [5]). The PASS birth cohort would allow us to better understand whether or not timing, frequency and quantities of alcohol exposure are able to predict which children have more cognitive and behavioral problems later in childhood, and the neural bases of these relationships as a function of access to resources in the environment.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

We propose four options for achieving the goal of ECHO through the National Longitudinal Surveys Program (NLS) of the Bureau of Labor Statistics. As mentioned below, NIH has been a funding partner in the NLS program for many years through support from NICHD. Given the space constraints for this RFI, we are submitting only a brief description of each option. Please contact me if you would like specific details on any of these options. The NLS are nationally representative surveys that follow the same sample of individuals from specific birth cohorts over time. The surveys collect data on labor market activity, schooling, fertility, program participation, health, and much, much more. We have two cohorts currently in the field. The older group, the National Longitudinal Survey of Youth 1979 (NLSY79), consists of individuals born from 1957 to 1964; they were 14 to 22 when first interviewed in 1979. The younger group, the National Longitudinal Survey of Youth 1997 (NLSY97), consists of individuals born from 1980 to 1984; they were 12-17 when first interviewed in 1997. The NLSY79 has been interviewed 25 times since the late 1970s, and the children of the women in this sample (the “Children of the NLSY79”) have been tested and interviewed 14 times since 1986; the NLSY97 has been interviewed 16 times beginning in the late 1990s. NICHD has supported the Children of the NLSY79. More information about the NLS is available at our website, <https://www.nlsinfo.org/> .

Additional core elements to be considered

Option 1 (short term): The NLSY79 data (the main sample and the child sample) already have rich data on mothers and their children. Information on the mother/child location at each sample round is available at a detailed geographic level (Census tract). In order to understand the role of environmental influences (such as pollution, crime, and access to services) on child health outcomes, one could merge the NLSY79 data with various environmental variables available at particular geographic levels. The NLSY79 also collects information about children’s home environments and mother characteristics.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

Option 2 (medium term): Unlike the NLSY79, the NLSY97 does not have a child component. The members of this cohort are in their 30's currently. Although some children have already been born to women in this cohort, other children will be born to these women at the time of future rounds of the NLSY97. For these rounds, we could add questions of the women and any children they might have, building on our experience with the Children of the NLSY79. Option 3 (medium term): The Children of the NLSY79 are currently a wide range of ages (approximately age 4 to 44). We could interview these individuals and ask about children they have had or may have in the future. This could be achieved through a modification of the existing instrument (individuals continue to be surveyed as young adults) or through a separate instrument given to this sample of individuals. Option 4 (long term): Develop a new NLS cohort with a child component (in the model of the NLSY79). This would allow the most attention to ECHO goals because (1) over time we would be able to capture all children born to a cohort of mothers and (2) we would be able to develop specific questions (in the mother and child questionnaires) about environmental aspects.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

[Respondent] is a small business specializing in design of electronic surveys and tools that collect, process and research questionnaire, statistical, clinical and medical science data. Working on NHANES (1996-2011) and NCS (2005-2015) we developed multiple study data management systems including DCAS (Data Collection Application Suite) – a government (NIH) owned survey toolset, used to collect majority of data on the NCS, and gained a lot of experience in data harmonization. On the NCS we worked with multiple academic study centers, two Regional Operation Centers and other stakeholders, we transitioned data from more than 20 different systems and harmonized data from multiple sources

for the delivery of unified SAS datasets. On NHANES we integrated data from more than 20 historical CDC and NIH studies combining them into a single metadata repository for cross study data comparison and research. We learnt several lessons for harmonizing data across cohorts: 1. All cohorts should use machine readable instrument specifications dynamically interpreted by all data collection systems in a consistent way and complying with the same data presentation and storage standards. 2. Machine readable instrument specifications should include all data elements needed to collect the data (including question text, response categories, data input constrains and instrument flow skips and branches), verify the data quality and generate statistical delivery datasets. 3. Minimizing the number of different data collection systems simplifies data harmonization and improves data quality. 4. Establishing unified training protocol and join training sessions for data collectors from all cohorts helps improve data consistency and simplifies data harmonization 5. Creating a set of unified data quality reports for both raw and harmonized datasets allows comparing data quality across cohorts. 6. Creating a metadata repository combining instruments from all cohorts allows to effectively identify fully, partially and non-harmonizable data elements by combining automatic and user-driven procedures.

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

[Respondent] is a small business specializing in design of electronic surveys and tools that collect, process and research questionnaire, statistical, clinical and medical science data. Working on NHANES (1996-2011) and NCS (2005-2015) we developed multiple study management systems including DCAS (Data Collection Application Suite), used to collect majority of data on NCS. DCAS is a government (NIH) owned survey toolset available without license fees. We gained a lot of experience working 10 years on NCS with multiple study centers, two ROCs and other stakeholders, producing over 300 questionnaires (available for future reuse and customization). We learned a few lessons in providing state-of-the-art adaptable study management solution: 1. Metadata describing questionnaires (including screen text, response categories, input validation rules, instrument flow, calculated fields, referencing previous responses, etc.) must be cleanly separated from the software and effectively maintained by non-IT personnel using a friendly point-and-click editor. 2. Questionnaire metadata must be interpreted on-the-fly by multiple fully interoperable data collection systems, supporting CAPI, CASI, CATI, SAQ, PAPI on Windows, Web, and mobile platforms in online/offline modes. 3. Electronic SAQs with BYOD (bring your own device) support allows decreasing data collection cost, improving response rate, data collection time and providing opportunities for new types of data collection: diaries, images, audio, video, geo-location, (bio/activity) sensor data, etc. 4. Data collection systems must support PHR/PMR integration and data standards (HL7/CDISC) for interoperability with other hospital systems and studies; provide secure data storage and transmission mechanisms protecting PII/PHR data in central storage, local devices and transit. 5. Participant/case data elements must be post-processed automatically from the questionnaire data and available immediately in a study case management system and subsequent questionnaires. 6. Data delivery and statistical (SAS) datasets must be generated automatically within short timeframe (days not weeks) 7. Study software should be open-source and open-architecture allowing easy integration with other systems and prevent NIH from vendor lock-in.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up

through childhood, available biologic or environmental specimens)
(*Submitter left answer blank*)

The additional IDeA States opportunity

(*Submitter left answer blank*)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Clear benefits from leveraging existing cohorts include time, cost efficiency, and the potential for generalizability. Establishing cohorts is very expensive, time-consuming, and logistically demanding, which likely impacted the lack of success of the NCS. While longitudinal follow-up of established cohorts also presents logistical challenges, it is more feasible and less expensive. Shared, standardized outcomes across cohorts will likely be geographically and racially diverse and collectively more generalizable to the U.S. population. By design, aspects of using existing cohorts will be retrospective and thus they will variably be missing important information to achieve the stated aims. To minimize this potential drawback, it will be necessary to state and define the minimum data necessary in any given existing cohort to be candidates for the award. For example, while there is a possibility of abstracting previous data from medical records, there are not usually ways to collect biologic samples retroactively. The heterogeneous nature of comparisons across multiple established cohorts, while offering generalizability, will require strict uniformity of definitions and data collection, as well as a careful analytic plan. One of the most important considerations will be the inclusion of maternal pregnancy data and specimens for analysis. Three of the four core elements simply cannot be studied without the inclusion of these vital data. Numerous recent studies have demonstrated that pregnancy and the in-utero environment influence outcomes across the lifespan of offspring. The origins of the outcomes of interest do not begin at birth, but at conception or even earlier. It will also be important for the existing cohorts to have the ability to continue to follow subjects within the cohort. In birth cohorts where mothers have enrolled and consented to a few short-term examinations or samples from the neonate, subjects can be contacted and consent to be in the long-term ongoing cohort.

Additional core elements to be considered

(*Submitter left answer blank*)

Considerations for harmonizing data across cohorts

Definitions and common data acquisition will need to be a central emphasis. This is a significant challenge even for a planned multicenter prospective study. Ideally, this will be accomplished prior to selection of the participating cohorts as 1) it will be part of the selection criteria and 2) it will prevent the wasting of valuable time over the life of the initiative (lessons learned from prior consortium initiatives). The topic of specimens and tissue samples will need careful consideration. A minimum (amount, range, quality) of available specimens for participants in the chosen cohort will be important to establish prior to selecting the cohorts. Another important consideration will be determining which specimen types will be necessary for which analyses. The process by which specimens are collected and stored significantly influences what studies and the number of studies they can be used for. As future issues and topics of interest cannot necessarily be anticipated, biological specimens should be collected that are appropriate for long-term storage. Data collected should be preserved with as many details as possible to allow for

future categorization, rather than categorizing data at the time of collection. Specific to the epigenetic analyses, questions as simple as which tissue to analyze from pregnancy (e.g. placenta, cord blood) will require careful consideration. Previous initiatives that have not prioritized this have been left without the necessary specimens to pursue mechanistic explanations for important observations. Throughout data collection and analysis, samples must be representative and both study recruitment and retention must employ best practices to ensure the quality of the study.

High impact areas of opportunity in addition to those listed

Neurodevelopmental outcomes, including cognitive, emotional, and physical metrics, though already highlighted, are all critically important and challenging to measure as most clinical assessments are not sufficiently rigorous for study. Participating sites would need to have the capacity to accurately measure these outcomes. Attention to the impact of the physical and societal environment will require environmental measures that may be deduced from biologic samples and collected through surveys of subjects, as well as available data on such things as air quality.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

The field of genetics is changing very rapidly. Both a priori planning as well as dynamic consultation should be employed to ensure that the questions being asked, the approach to asking them, and the methodology used to analyze them are correct and relevant. Advances in imaging will continue to evolve, particularly relating to pregnancy, where advancing non-invasive imaging modalities have enabled studies among this vulnerable population that have previously been impossible. Ideally, the consortium will consider both the importance of imaging and its evolving nature.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Human Placenta Project could be a useful resource. Preconception data, coupled with pregnancy and maternal predictor variables, would be extremely beneficial for studying all four of the proposed focus areas.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Benefits: maximizes resources already expended Drawbacks: existing cohorts will need to be carefully selected, to ensure diversity of sample types and ensure that the existing cohorts can recruit and retain participants in the follow-up period. Including only samples biological families will bias the results and confound shared genetic effects with environmental effects.

Additional core elements to be considered

Schools (and the teachers and peers within them) effect every child in the US (aside from homeschooled). Cohorts that have data on the school environment would be especially useful.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

We suggest an existing research study that could address multiple focus areas in the RFI. The dataset is the Early Growth and Development Study (EGDS), which is a nationwide sample of 561 children who were adopted at birth (Leve et al., 2013). The sample also includes their adoptive parents, birth parents, and 200 biological siblings of the adopted children who have been reared by the birth mother. This longitudinal study has previously been funded by NICHD, NIDA, NIMH, and NIDDK. Just over half of the children are male (57.2%), and the sample is ethnically diverse with 55.6% Caucasian, 19.3% multi-racial, 13% African American, 10.9% Latino, and 2% other. Children currently range in age from 6 – 12 years old and have been assessed nearly annually since birth, with retention rates above 80%. Major behavioral health outcomes include mental health, neurodevelopment, school achievement, obesity, social skills, and executive function. Biological specimens include DNA from adoptive parents, biological parents, and children, and salivary cortisol from children and birth parents. Birth medical records have been collected and coded. Postnatal environmental exposures include neighborhood, parenting, marital relations, peers, schools, and diet/food diary. Prenatal environment such as substance exposure and stress have been also assessed. The EGDS provides an excellent method of testing environmental exposures that are not contaminated by shared genetic influences or by prenatal influences because the children have been reared since birth by parents who are not genetically-related to them and did not provide the intrauterine environment. This allows stronger conclusions to be made about environmental effects on children's health outcomes. Leve, LD, Neiderhiser, JM, Shaw, DS, Ganiban, J, Natsuaki, MN, & Reiss, D. (2013). The Early Growth and Development Study: A prospective adoption study of child behavior from birth through middle childhood. *Twin Research and Human Genetics*, 16, 412–423. PMC: 3572752

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect

standardized data elements

The global burden of disease is due mostly to chronic diseases and conditions with origins in early life. Primary prevention represents the best hope to effectively reduce the global burden of chronic disease for both children and adults. We believe the ECHO program should focus data collection and implementation strategies on reducing the impact of environmental influences in utero and the first two years of infancy, “the first 1000 days.” The Core Elements and Focus Areas should clearly address how these areas can inform the developmental origins of chronic disease and how the selected childhood outcomes represent risk for disease throughout the life course. Taken together, ECHO should represent the NIH’s commitment to develop a comprehensive strategy for the primary prevention of chronic diseases and conditions in both children and adults.

Additional core elements to be considered

In regards to the core elements of the study, the use of multiple independent cohorts with coordinated core elements is an appropriate strategy. We respectfully request that you create new cohorts and/or recruit new mother/infant pairs into selected extant cohorts. This hybrid strategy will allow investigators to assess new environmental exposures that did not exist when extant cohorts were created. It will also permit the study of high-risk or high-interest populations that are not covered by extant cohorts.

Considerations for harmonizing data across cohorts

Lastly, we urge that the environmental assessment data that is collected by the ECHO program be comparable to the assessment data being developed as part of the Precision Medicine Initiative cohort study.

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

3D facial photographs. It has been known for over a half century that facial features can predict the brain (DeMyer et al, 1964) and more recent studies utilizing 3D dense surface models of face shape have been able to accurately recognize a variety of neurodevelopmental disorders (e.g. fetal alcohol syndrome, autism, genetic disorders) as well as brain anomalies (Hammond, 2014). This is not unexpected, since the development of the face is closely linked to the development of the brain. While there are certainly issues of confidentiality that would have to be addressed, as this approach matures and analytical techniques become more sophisticated, it might provide a simple screening technique for specific behavioral and genetic syndromes. It might also be useful in the field of telemedicine, identifying specific syndromes among populations where specialists might not be available. The cost of this technology has decreased significantly in the last few years, and the expectation is that it will continue to decrease as technology advances. Another consideration might be the availability of animal and cellular models related to the area under study. In our experience in the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), we have found that partnering basic scientists with those working on human cohorts has greatly enhanced our understanding of Fetal Alcohol Spectrum Disorders. Therefore, we would encourage you to provide support for such partnerships within ECHO.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

While it might be considered under neurodevelopment, fetal alcohol spectrum disorders was not specifically mentioned. Over 60% of women consume alcohol and 13% consume more than 7 drinks per week. Many of these women expose their developing embryo to alcohol even before they recognize they are pregnant; about 8% of pregnant women continue to drink after pregnancy recognition, and about 1.5% of pregnant women binge drink, which is particularly dangerous. Prenatal alcohol exposure is a leading cause of intellectual deficiency and behavioral problems, with rates at least as high as autism. While it is difficult to know with certainty the number of children born with FASD each year, numbers between 40,000 and higher have been quoted. Prenatal alcohol exposure has also been linked with a variety of adverse long-term health consequences (metabolic syndrome, auto immune dysfunction, various cancers,) in animal model studies. Importantly, several cohorts already exist, both in the US and abroad. In sum, alcohol is a common in utero exposure, there is ample literature suggesting it can have major developmental impacts on organ systems, and cohorts already exist.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) is an NIAAA supported consortium (U mechanism) that has been collecting a variety of data on children and adolescents with histories of moderate and heavy prenatal alcohol exposure, as well as typically developing controls, and a smaller number with other cognitive/behavioral problems. Over 2700 records are in our secure database, including demographic data, dysmorphology exams, comprehensive neurobehavioral

assessments, close to 1000 facial images, genetic data on a more limited number, and nearly 600 structural and/or functional brain scans. We have been successful in maintaining contact with a majority of this cohort, as we are now doing longitudinal brain scans, and subjects participate in neurobehavioral assessments during various times of development.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

Climate change is the most important environmental health problem confronting society. We believe that some of the funds from the ECHO program should be used to support research related to the impact of climate change on children's health. Such research might look at the impact of climate change on pregnancy and the outcomes of pregnancy, the impact of climate change on developmental and behavioral outcomes, the impact of climate change on childhood nutrition, the impact of climate change on pulmonary disease (asthma and other problems), the impact of climate change on childhood infections and a number of other issues. Much of this research could be undertaken using existing or newly developed cohorts. Hospital systems like Inova across the U.S. are working towards increasing preparedness for health impacts associated with climate change. Much, however, remains poorly understood. Further research is needed if institutions such as Inova can serve and protect their communities effectively. Children are at uniquely elevated risk from climate change health impacts.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Utilizing extant cohorts for this research has many potential benefits including the ability to optimize resource allocation to projects with demonstrated recruitment success. One drawback is that standardization of data collection across studies could be complicated. This argues in favor of prioritizing cohorts that are still in the early phases of data collection and recruitment in order to optimize the ability to collect as much standardized data across sites as possible. One excellent example of a cohort study that is being conducted in a resource-rich environment, enjoys significant institutional support, and would be quite flexible to standardization, and is likely to yield a large sample of complete data starting in the prenatal period is the All Children's Hospital-Johns Hopkins Medicine (ACH-JHM) Prospective Research on Early Determinants of Illness and Children's health Trajectories Study ("PREDICT Study"). The PREDICT Study was launched at ACH-JHM in St. Petersburg, Florida in January 2015. PREDICT seeks to provide critical insight into effective population- and individual-level disease prevention strategies by collecting data necessary to describe the timing and nature of pre- and post-natal factors that are associated with key pediatric health outcomes including poor birth outcomes, obesity, and developmental delay. PREDICT has two sub-cohorts: A birth sub-cohort that enrolls pregnant women at 12+ weeks gestation, and an early childhood sub-cohort of children from birth to <6 years.

Additional core elements to be considered

Requiring collection of the full range of environmental factors including measures of the social and physical environment in addition to toxic exposures and in utero exposures seems critical to advancing our understanding of the complex relationship between environmental factors and other biological factors on child development and disease risk. Funding extant cohorts that already include measures of the family and social environment is critical as is a commitment to funding studies that have the ability to measure environmental toxins, metabolomic, and genomic factors. The PREDICT Study is already designed with this array of measures in mind. PREDICT is, to our knowledge, the first institution-wide prospective inception cohort study and associated biorepository focused on healthy children in a clinical setting. Not only is PREDICT unique in its design for investigating proteomic and metabolomic pathways, but this data collection occurs alongside rich and robust characterization of children's social and physical environments, the exposures upon which disease risk or resilience may ultimately depend.

Considerations for harmonizing data across cohorts

Identifying cohorts with standardized data collection procedures that also have significant ongoing potential to recruit prenatal and early childhood cohorts seems critical to insuring that the approach of investing in existing cohorts yields significant and robust data that can be analyzed across all sites. As state above, this argues for investing in sophisticated and proven cohorts that are also at early stages of data collection so that they are flexible and nimble to measurement modifications needed to achieve harmonization. The PREDICT Study exemplifies the type of studies needed to make harmonization possible and high-yield. PREDICT is an effective protocol for recruiting a birth cohort and an early

childhood cohort. It has demonstrated significant success in recruiting participants in its first year. Yet because the cohort is early in the data collection process, it is also well-positioned for addition of new measures and harmonization of measures with other sites. PREDICT takes advantage of ACH-JHM's extraordinary investments in the next generation of pediatric research, including research cores in proteomics, and metabolomics, as well as one of the most advanced research biorepositories in the country. Critically, PREDICT has been designed from its inception to collect, prepare, and store biosamples to fully leverage their use with these techniques. This study also benefits from the ability to access medical records for participating children over time because PREDICT follows pregnant women and children prospectively in a primary care setting (OB care and pediatrics), which provides medical records for participants.

High impact areas of opportunity in addition to those listed

Utilizing this type of comprehensive data to better understand the complex factors that impact child obesity risk is critical. Beyond obesity risk, it seems critical to identify early life risk factors for cardiovascular disease. Understanding obesity is one route for assessing this, but there may be additional risk factors associated with chronic environmental exposures over time that can also be elucidated through investing in harmonization of measures across extant cohorts. PREDICT is well-suited to this and already has measures from across the spectrum from biospecimens to assessments of the neighborhood social environment. Such a comprehensive view is needed to better understand what puts children at risk for obesity and cardiovascular disease, what factors make some children resilient to these risks, and how we can intervene to reduce risk early among high risk populations. Having access to clinical data over time for patients is useful in addressing this issue, which is one of the many benefits of the The PREDICT Study design.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The chosen four focus areas seem timely, important and relevant to long-term health outcomes for children. In fact, obesity, neurodevelopment, and pre-, peri-, and post-natal outcomes are all key foci for the PREDICT Study. They also necessitate a comprehensive approach to assessing risk exposures and intermediate outcomes. The robust and comprehensive nature of the data collected in PREDICT--ranging from biospecimens to measures of children's social and physical environmental exposures and clinical outcomes--makes it ideally suited to investigating multiple health outcomes prioritized by ECHO. A priori, it is designed with birth outcomes, obesity, and neurodevelopment in mind. But it could also offer opportunities to augment data from other sites investigating upper and lower respiratory diseases, particularly because of the rich combination of data regarding toxic exposures and clinical outcomes that can be gleaned from the biorepository specimens and clinical outcome data respectively. PREDICT has two sub-cohorts: a birth sub-cohort that enrolls women at 12+ weeks gestation, and an early childhood sub-cohort of children from birth to <6 years. PREDICT is designed to follow children over time to collect both ongoing information on family, social, and physical environmental exposures and to collect biospecimens from participants. It is also designed to extract data from the participants' medical charts at scheduled intervals, which is extremely helpful in assessing the overall health of participants

including any medical diagnoses they receive at different points in their growth and development. PREDICT also takes advantage of ACH-JHM's extraordinary investments in the next generation of pediatric research, including research cores in proteomics, and metabolomics, as well as one of the most advanced research biorepositories in the country. Critically, PREDICT has been designed from its inception to collect, prepare, and store biosamples to fully leverage their use with these techniques.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

[Respondent] supports the intent to leverage existing cohorts to the greatest extent possible. However, some extant cohorts have shortcomings: for example, previously biobanked specimens may not include blood or tissue for chemical or biological analysis, necessitating a potentially expensive add-on component. Cohorts of pregnant women are likely no longer pregnant or recently post-natal, thereby limiting the usefulness of current specimens. We urge NIH not to limit cohorts under the ECHO program only to those that were funded in the original National Children's Study. Any cohorts used in the proposed projects must be distinguished by up-to-date methods of phenotyping and specimen storage so as to achieve the aims of each project. Such a restriction would put the ECHO initiative at risk of the same failures in cohort assembly and phenotyping that plagued the NCS. We encourage openness to international cohorts that provide unique opportunities as controls for environmental factors under study in US-based cohorts. Finally, while we recognize the value of cohorts, we also recognize the challenges associated with such tools as well as the existence of other tools and technologies to help obtain the necessary information. As such, there may be some value to considering investigator-initiated research that might exist without a cohort.

Additional core elements to be considered

Integration of basic science within ECHO is paramount to ensure that mechanistic and epidemiologic approaches synergize and capitalize on data and biospecimens gathered from the project. [Respondent] urges that a strong emphasis on genetics be coupled with epigenetics as a core element to be addressed across all studies. Many of the core elements derive from patient history and cannot be independently validated: e.g. "maternal exposome". Absent a robust incorporation of genetics, the follow-on study will not differ significantly from the original NCS and will fail to achieve the scientific promise of the "omics" revolution (genomics, proteomics, metabolomics) in personalized medicine and population health. One aspect of support for basic research could include direct funding for essential shared core research infrastructure (e.g., high-throughput sequencing, bioinformatics, data analysis) and for training of early-career investigators. By supporting the integration of basic science within the larger project, NIH can help ensure that data, biospecimens, and analytic technologies necessary for completion of ECHO projects are available to all investigators and thereby accelerate improvements in child health. Whether all studies and cohorts proposed for funding by ECHO must address all components of the core elements needs clarification. For example, including microbiome information (see Typical early development) may be impossible for extant cohorts assembled 5 years ago.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

ECHO needs to recognize that the arc of development encompasses pre-conception through in-utero development, post-natal, childhood and adolescence and that genetics and the environment exert synergistic influences on such development. We strongly encourage NIH to recognize the impact of genetics by ensuring its inclusion among the core elements and focus areas proposed in the RFI. The incorporation of genetic information as an area of opportunity is critical to ensure that histories of environmental exposures (phenotypes) are validated by hard data.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

We recommend that NIH not mix organ-specific areas (upper and lower airway) with conditions such as obesity and postnatal outcomes. Organ-specific approaches limit focus on broad mechanisms, such as the immune system, that link environment to health outcomes. Study of allergies should not be confined to the lung and should include the complete biology of the disease. For example, food and skin allergy can manifest as eosinophilic esophagitis (EoE), a chronic disorder of childhood associated with airway hyper-responsiveness and asthma. Revised focus areas: Growth and Obesity: Add extreme phenotypes, prenatal influences, behavioral risk factors. Pre-, peri- and postnatal outcomes: Add complications from prematurity, growth. Revise Upper and lower airways as Interaction of immunity and environment (e.g., allergic responses of lung, skin and intestinal tract; asthma; sleep-disordered breathing) Selected potential study resources at CCHMC: Asthma: Birth cohort of 762 allergic or asthmatic children with at least one parent who is skin-test positive for an aeroallergen. Exposure to traffic-related particulate matter at home, daycare, or babysitting sites determined by land use regression. Phenotyping of household for mold, water, and dust analysis. DNA samples genotyped on a custom SNP array including genes related to asthma, eczema, and nicotine metabolism. Pre-term birth: 400 pre-term and 947 term mother-infant dyads from Finland with extensive demographic information, including maternal characteristics, drug exposures, smoking and reproductive family history; 900 families have been genotyped. We also possess 103 pre-term and 108 term U.S. mother-infant dyads with DNA samples and extensive demographic information. Eosinophilic esophagitis: Cohort of 896 children diagnosed with EoE genotyped for 5 million genetic variants. Detailed phenotypic information plus environmental exposure history through disease-specific and clinical research databases. With 4000 endoscopic tissue biopsies available, this cohort offers the rare opportunity to study the diseased tissue and to develop paradigms about gene-environment interactions at the tissue level.

The additional IDeA States opportunity

[Respondent] recognizes the challenges associated with recruiting pediatric patients from underserved rural regions for clinical trials. We support training of clinical trialists in IDeA states and locations to expand recruitment and engagement of pediatric patients in clinical trials. Simultaneously, we

encourage NIH not to limit this activity solely to research institutions located in IDeA states. For example, ~20% of our patients come from a neighboring IDeA state, and our clinical trials network includes institutions in such states. We recommend that NIH give equal preference to institutions with clinical recruitment networks and the infrastructure to gather clinical data in IDeA states and not limit this opportunity only to institutions physically located in such states.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

A key area of consideration is harmonization across studies on methods for collecting and analyzing key predictors and covariates across existing cohorts for both traditional markers of exposure (e.g. consistent biomarkers in consistent matrices) as well as emerging exposures (e.g. contextual psychosocial factors including consistent measurement of mental health outcomes, child behavioral outcomes as well as more complex genetic, epigenetic and transcriptional markers). ECHO also opens a window of opportunity for development of new biomarkers associated with the microbiome. To better address chronic disease risk later in life and improve child growth and development there also needs to be increased emphasis on studies that look both at vulnerability (i.e., who has highest body burden) and determinants of vulnerability (social risk factors) as well as susceptibility (i.e., which groups are inherently more at risk due to genetics, or changing susceptibility overtime due to differences in vulnerability, for example- improved understanding how poverty changes metabolism and toxicokinetics to increase risk of disease from exposure). Understanding vulnerability will require increased infusion of resources for analysis of new and novel chemicals and emerging toxicants in addition to traditional pollutants (metal, toxins, organics). Studying susceptibility will require big data, new methods for collecting transcriptional biomarkers and consistency in this measurement across multiple studies. Furthermore, more sophisticated statistical and analytic methods are needed to conduct studies of effect modification and mediation in existing studies that may be under-powered to address interactions well. Children are particularly vulnerable to adverse exposure to environmental chemicals because of their smaller body weights and hand-to-mouth behaviors, but we don't understand these differences by gender or poverty status well, or if these relationships are well established- the mechanisms underlying these interaction are not well understood. Consequently, increased efforts to track changes in exposure and health longitudinally in these cohorts will be important.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

The obvious advantage to leveraging existing cohorts is the time and cost headstart that comes with established cohorts. Many existing cohorts are decades old and have used standardized and widely accepted tools (for example International Study of Asthma and Allergy in Children (ISAAC) questionnaires) to collect data and samples and thus may fit well into programmatic objectives.

Furthermore, in many instances it will be possible to fill in missing information utilizing tools such as public records of environmental monitoring data and blood spots collected onto Guthrie cards for newborn screening. Another aspect of existing cohort design to consider is the power of multi-generational cohorts. Environmental exposures affect at minimum 2 generations (the exposed individual and their germ cells that will produce the next generation) and thus are critical for understanding the environmental impacts on health outcomes. This is especially the case in conditions whose incidence and/or prevalence have risen in recent decades as is the case with childhood asthma, allergies, obesity, autism and ADHD; thus the value of multi-generational cohorts is particularly high for investigating these conditions. There are a number of U.S. scientists who are actively conducting research on cohorts that are outside the U.S. Some of these non-U.S. cohorts have direct relevance to U.S. populations in terms of understanding environmental influences on child health outcomes. Thus, including relevant non-U.S. cohorts with studies conducted by U.S. researchers is recommended.

Additional core elements to be considered

An additional Core Element to consider for inclusion is that of pregnancy conditions and environmental exposures during the prenatal period. Information about pregnancy conditions will allow the identification of ways to interrupt the transmission of parental risks to the next generation. While there is a 'suggestion' of these elements as part of the "maternal exposome" under the Core Element "epigenetic influences on early childhood development," the outcomes of this program would be improved if pregnancy conditions and environmental exposures during the prenatal period were explicitly included as a Core Element. While the Core Element "Typical early development" lists the microbiome, we encourage the explicit listing of microbiome under "Environmental factors" as well. Microbiome can be interpreted widely encompassing microbial communities experienced during pregnancy, during the neonatal period and during further growth and development. While some specific hypotheses have been tested regarding gut or lung communities, the recent understanding of effects of gut microbes on brain (gut-brain axis) suggests that other linkages will be discovered and found to be related especially to tolerance and immune system development that can have a big impact on child health outcomes in all of the focus areas. A key feature of future efforts should be to take steps to form

and test mechanistic hypotheses, especially related to microbiome allergic outcome events. Although current evidence is meager, there are data that suggest mechanistic links between the microbiome and epigenome and between the epigenome and immune status. In general, mechanistic hypothesis testing should be favored as a means to identify new strategies rather than incremental strategies for new critical control points. Some risk should be acceptable if the reward potential is large. This strategy of mechanistic testing could provide whole new pathways to explore for control and treatment that have not yet been conceived.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

The renaming of the Focus Area “Upper and lower airway” to “Upper and lower airway and allergies” is suggested. This explicit inclusion of “allergies” will allow this focus area to also include atopy (aka allergic sensitization) and atopic dermatitis, which are conditions that frequently precede and lead to asthma. Atopic dermatitis is in itself an important child health outcome and it — along with atopy— is undeniably linked to the potentially life threatening conditions of asthma and food allergy. The explicit inclusion of immune processes as an additional focus area is suggested. Immune processes are closely related to many outcomes in each of the focus areas. Immune processes and their related epigenetic effects are relatively easy to determine during pregnancy and in cord blood and will aid the development of better prediction models.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

This program will by design involve studies of cohorts that are likely to be large, multi-centered and complex, with the results requiring cross-cohort validation. As such, high-level expertise in the area of data analysis will be needed. This should be explicitly stated in the program design and included in Coordinating Centers. The data analysis expertise required should include not only the selection and application of appropriate statistical tests but also the ability to design new data analysis methodology, as needed.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The three-generational (F0, F1, F2) Isle of Wight, UK birth cohort study contains 1,436 participants in the F1 generation, who were born in 1989-1990. Detailed questionnaire information and maternal blood is available from the F0 generation. Detailed information and samples have been collected from the F1 generation at ages 1, 2, 4, 10 and 18 years including standardized questionnaires, blood, DNA, skin prick tests and lung function tests. Similar data and samples are currently being collected from the F2 generation, which numbers more than 300 children to date. The outcomes studied in this cohort are asthma and related allergies. Environmental exposure information includes the pregnancy period and includes specific exposures such as pets, vaccinations, oral contraceptive use, and tobacco smoke along with other common indoor and outdoor environmental exposures.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

The Lifestyle Interventions for Expectant Moms (LIFE-Moms) Consortium spent the first year of funding harmonizing and standardizing data across the seven trials. There were many important lessons learned in that process. First, it is important to prioritize the data to be collected to address staff, participant and financial burden. Adding common measures in addition to the collection of local data resulted in significant burden not foreseen during the design process. Second, multiple factors should be considered when deciding on the commonality of inclusion/exclusion criteria and the impact this may have on new recruitment within each study. Third, a central data management system should be specified in the RFA for the collection of all new data. LIFE-Moms did not mandate this and has invested a significant amount of time on the part of the Research Coordinating Unit and each of the three sites who chose to transfer their data on a weekly basis. While this lists only a few of the issues we encountered that first year, we are more than willing to go into more detail with NIH if interested.

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Lifestyle Interventions for Expectant Moms (LIFE-Moms) Consortium is an extant cohort designed to determine, in pregnant women with overweight or obesity, whether various behavioral and lifestyle interventions reduce excessive gestational weight gain and subsequent adverse maternal and neonatal outcomes, and obesity in offspring. The LIFE-Moms Consortium is a collaboration among seven clinical centers, a Research Coordinating Unit, and the NIH designed to support each clinical center's conduct of a separate trial of a unique intervention. Specific common measures, procedures, and eligibility criteria are consistent across the 7 trials allowing data to be combined and/or compared readily. Recruitment of 1,164 participants is expected to be completed by Fall 2015 with mothers and children being followed currently until 12 months postpartum. The LIFE-Moms Consortium is racially diverse with 35% African

American and 24% Hispanic. All children will have intra-uterine exposure to overweight or obesity and form an ideal cohort to extend follow-up past one year to evaluate the long term outcomes of obesity and metabolic abnormalities in the children as well as additional environmental exposures. Several biospecimens are being collected currently, thus allowing for the analyses of additional prenatal exposures: blood and urine on mothers at study enrollment (9-15 weeks gestation) and 35-36 weeks gestation, cord blood on infants at birth, and placentas (subset only).

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

MUST STUDY NEW BIRTHS: The strategy of using extant birth cohorts for data pooling and facilitating methods development research is an appropriate first step, but it is not a sufficient strategy to study the effects of environment on children's health. The long-term ECHO program strategy must include studying new births of a sufficient number using a common data collection protocol to allow for assessment of environment-gene interactions during key periods of developmental vulnerabilities.

CRITICALLY EVALUATE LIMITATIONS OF DATA POOLING: NIH should critically evaluate past efforts to pool data across cohorts. Studies generally have collected data and specimens in a way that makes pooling data difficult. For example, pooling data among the NIEHS-EPA children's centers has been very difficult and unable to address a number of research questions. One reason is that mature cohorts were not designed to collect information on some contemporary exposures, so questionnaire information and archived specimens may not be useful for new exposures. Studies in Europe have already used the proposed ECHO program strategy. The incremental scientific value in doing the same thing with US cohorts, which generally are smaller and less homogeneous, should be critically assessed early in this program before too much funding is expended. **USE OF CORE DATA COLLECTION PROTOCOL:** Developing a core data collection protocol is worthwhile, but the primary focus should be developing a protocol for use in new cohort studies. Studies must use concurrent data collection, especially for measuring exposures to transient environmental factors such as non-persistent chemicals, to maximize measurement validity. However, many extant cohorts are well underway, so it's too late to use a new protocol to study critical early periods of development. Enrolling subsequent births of existing cohorts will not be efficient because mothers in older cohorts have low rates of new births.

Additional core elements to be considered

INVEST HEAVILY IN ENVIRONMENTAL EXPOSURE ASSESSMENT: We agree with the RFI statements that a major focus of the ECHO program should be development of tools to enhance measurement of environmental exposures. The program must assure that the core definition of the environment includes assessments of exposures from chemicals and toxic components of air, water, food, occupational activities, and consumer products. The program must invest in sophisticated exposure assessment methods and technologies that include collection of environmental specimens; use of air monitoring, drinking water quality, and pesticide use data; GIS; and modeling of environmental exposures over time. Direct measurement of environmental exposures is critical; many scientifically important exposures cannot be determined using only questionnaires and archived biological specimens. The program should invest in research to enhance existing environmental exposure

assessment technologies and modeling in which new measurements and time-activity data can be linked to extant environmental data for robust exposure assessment. Consideration must be given to scaling up methods, so they become cost effective to use in large study populations.

Considerations for harmonizing data across cohorts

SUPPORT NEW EXPOSURE ASSESSMENT, NOT JUST DATA POOLING, IN EXTANT COHORTS: While there are substantial limitations to pooling data from studies that were not designed for such purpose, there still may be an opportunity to estimate or model exposures to some important environmental exposure domains, such as air pollution, based on data in studies even if the studies did not collect the data. One example is European Study of Cohorts for Air Pollution Effects (ESCAPE), a study in the European Union, which provided funds to do exposure assessment on air pollution, traffic, and traffic-related noise in existing cohorts using a standardized protocol. This project has had high scientific and policy impacts. The ECHO program should evaluate these EU programs that funded new exposure assessment research using existing cohorts and evaluate whether this strategy should be used in the US. It still must be recognized that this exposure assessment strategy cannot be used to study the effects of transient environmental factors, such as non-persistent chemicals, which requires concurrent measurement of environmental exposures in new cohorts. The strategies and methods for exposure assessment must be designed appropriately based on the nature of the environmental factors and toxicants.

High impact areas of opportunity in addition to those listed

FOLLOW OLDER COHORTS UNTIL ADULTHOOD: We concur with the RFI on the importance of following older birth cohorts to study the effects of environment on later development. Identifying the long-term consequences of early childhood experiences is critical to understanding determinants of health and disease across the lifespan (e.g., Developmental Origins of Health and Disease model). Priority should be given to collaborating with extant cohorts that collected and archived both environmental and biological specimens beginning during the prenatal period. **UTILIZE STRATEGIES FOR COST-EFFECTIVE COLLECTION OF DATA IN NEW COHORTS:** The ECHO program should consider three important opportunities that would allow for the cost-effective collection of data for new birth cohorts: (1) Utilize electronic medical records that are now more readily available under the Affordable Care Act and, in addition, retain biological specimens routinely collected during pregnancies (e.g., prenatal urines and bloods). (2) Maximize data and specimen collections that are on-going at HMOs (e.g., Kaiser or Geisinger), which have integrated perinatal and pediatric data systems by collecting exposure-related information or to collect specimens with maximum future benefit for exposure assessment. (3) Extend the proposed “Precision Medicine” cohort of 1 million to include women of reproductive age and, in doing so, potentially enrolling more than 10,000 in a birth cohort.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

DEVELOP NEW ENVIRONMENTAL EXPOSURE ASSESSMENT METHODS AND TECHNOLOGIES: The program is an opportunity for methodological innovation in designing and implementing new birth cohorts with prenatal enrollment and data collection using new and innovative exposure assessment technologies and methods. A key deliverable for the ECHO program scientific Coordinating Center and collaborating investigators should be to develop a core data collection protocol and recommended study design for implementing new birth cohort studies. The proposal should then be reviewed independently from NIH by a scientific panel, such as the NRC-IOM could convene. The NIH could then issue a RFI to establish a consortium of new birth cohort studies, which would use the common core protocol to study diverse populations and environmental conditions. Proposals for new studies should be awarded competitively and not be limited to the extant cohort investigators and organizations initially included in the ECHO

program. FURTHER DEVELOP EXPOSOME PARADIGM. The program should invest resources in further understanding the exposome, which includes validating and developing new measures. NIH needs to commit effort and funding in developing the exposome on the scale spent in developing methods to study the genome.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

EXAMPLES OF EXTANT COHORTS THAT COULD BE USED: Studies that could be used include cohorts from the NIEHS/EPA children's environmental health centers including the CHAMACOS study, the Home Study, the Columbia University study, as well as other long term cohort studies, such as the New Bedford study and Project Viva. The Collaborative Perinatal Project and the Child Health and Development studies could also be utilized for multiple generations, although these two studies have very little specimen that has been collected other than serum. As previously mentioned, most of these cohorts collected most of their data and specimens over the last decade or more, so the archived specimens may not reflect exposures to chemicals of current research interest. In addition, the NIH may retain specimens from the Vanguard pilot studies of the former National Children's Study. Investigators from several former NCS Vanguard Study centers maintained the ability to follow their former pilot cohort participants.

The additional IDeA States opportunity

This funding mechanism could be applied to support innovative, contributory research in selected locations (such as RI, SC, PR, etc.) where there is appropriate expertise to do so. Integral to this initiative should be an expressed commitment to supporting development of the next generation of investigators, including women and minorities.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Leveraging existing cohorts is a cost-effective and time-efficient approach; however, some clear characterization is needed to identify key components of possible cohorts (e.g., size, ages, ethnic/racial diversity, number of occasions of measurement, geography). This will facilitate an evaluation of the likely value of the cohort to the overall aims and will provide some means to establish a diverse (or concentrated) portfolio of studies (e.g., insuring that multiple cohorts are included that track infants and young children; insuring that an adolescent cohort is included to address health needs particular to adolescents). We would place special emphasis on frequency of measurement because study of developmental (within-individual) change is essential for drawing conclusions about exposures and health.

Additional core elements to be considered

The core elements are sound. We would, however, suggest that there is greater specificity as regards psychological/psychosocial factors, which compose part of the "Demographics" and "Environmental factors" components. That is, there is now a great deal of interest in social class/SES gradients of health,

but the value of these studies is quite limited because the measure of SES (typically education or income) is too vague and non-specific to discern causal effects or constitute a basis of intervention. We would strongly argue that measures of demographics of psychosocial context that are thought to index stress exposure be measured in a detailed manner with application to social policy (income to needs ratio, for example) and that these broad SES-like measures be complemented with proximal measures of stress that have ready translation to clinical practice and intervention models (e.g., for children, this could include caregiving quality and family stress).

Considerations for harmonizing data across cohorts

Although it is clearly valuable to harmonize data across studies, the methodologies developed for meta-analysis provide some flexibility and imply that methodological diversity should be welcome, at least to some degree. So, for example, the use of effect sizes as the unit of analysis and analytic approaches that consider risk/clinic status as a predictor of effect size provide two models for how data across diverse studies might be harmonized.

High impact areas of opportunity in addition to those listed

In addition to the areas already identified, we would suggest that emphasis be placed on biological factors that may act as mechanisms for a range of diseases and disorders that transcend medical and academic discipline. Some examples include the HPA axis, which has been implicated in psychiatric, cardiovascular, immunological and metabolic conditions; inflammation, which has been implicated in immunological, cardiovascular, metabolic, and psychiatric conditions; autonomic nervous system function, which has also been implicated in the same above conditions. A focus on biological mechanisms that pertain to the pathophysiology of multiple disorders would offer the strongest potential impact for health-relevant research.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

One of the major obstacles in translating research findings to clinical/practical application is that, in many cases, the lauded measurement methodology is terribly demanding in terms of time, money or expertise. And, the added value of expensive, technologically sophisticated measures may not offer much practical advantage to simpler approaches (e.g., complicated searches for biomarkers may add little to clinical interview). We therefore suggest that practical factors be considered when judging a data collection process. Furthermore, we would strongly suggest that considerable emphasis be placed on behavioral assessments that can be applied to clinical/practical use.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The Family Life Project is a prospective longitudinal study of over 1,000 children who were selected because of an initial interest in the effects of rural poverty on academic, health, and behavioral outcomes. Children have been studied using in-person assessments since 7 months of age (the children are now age 11 years old) using a variety of intensive observational, interview, and biological measurement approaches. Importantly, demographic and psychosocial measures are complemented with detailed, developmentally sensitive measures of caregiving and family conflict; salivary and blood samples to assess genetics, immunity, and neuroendocrine function; and extra-familial factors including schools and other social environments.

The additional IDeA States opportunity

We applaud the proposal to develop a national pediatric clinical research network and the efforts to develop and explore novel and model interventions embedded within existing cohorts. We would also suggest that the Family Life Project is one project that would have the kind of detailed and broad health and behavioral measures to contribute significantly to this effort, and contribute to pediatric research on health and obesity, neurodevelopment, behavioral and emotional problems, academic achievement.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

[Respondent] supports leveraging existing cohorts to maximize the use of existing resources and avoid potential duplication. We agree that developing ways to synergize and leverage existing data sources and biospecimen repositories represents a powerful strategy to impact children. We support the idea of standardizing data elements and using standardized questions. We think there would be great value in NIH providing concrete definitions regarding the use of extant cohorts and inventorying existing cohorts that could be used in follow-on projects. This inventory could be used to create a master list of known cohorts that meet certain quality and accessibility standards so the pediatric research community can fully understand available resources as well as gaps or deficiencies that may need to be addressed by augmenting existing resources or creating new cohorts. It is also necessary to develop a strategy to link existing databases from a variety of systems with one another and with Electronic Health Records. This includes but is not limited to: - Hospital birth record data; - Newborn screening results to provide baseline measures; - Developmental assessments performed by early intervention; - Longitudinal school outcomes data (state/city-wide reading tests, etc.); - Laboratory databases (e.g. LapCorp, etc.) for particular outcomes/exposures (for example, lead test results, hemoglobin, lipid profiles, etc.); and - Immunization registry data. Additionally, it is important to ensure that any tools and measures utilized are appropriate for special populations, as tools for typically developing children may not always be appropriate for children with specialized needs.

Additional core elements to be considered

According to McGinnis, et al., "Drawing on the power of the extensive studies of the past generation, we can now speak about our health prospects as being shaped by our experiences in five domains: genetic and gestational endowments, social circumstances, environmental conditions, behavioral choices, and medical care. The health of populations is the product of the intersecting influences from these different domains, influences that are dynamic and that vary in their impact depending upon when in the life course they occur and upon the effects of preceding and subsequent factors."

(<http://content.healthaffairs.org/content/21/2/78.full>) In considering these five domains, we suggest a further focus on information related to social determinants of health. Factors such as food hardship, poverty, family structure/resources, aversive and traumatic experiences, school quality, transportation options, neighborhood conditions, community violence, etc. should be collected as core elements. Additionally, we see a need for support for research to advance understanding of the impact of the environment on children's healthy development and on achievement of optimal health outcomes. Specifically, basic, translational, clinical, behavioral and delivery science research should be utilized. This includes funding to assist research institutions in attaining shared core research infrastructure necessary to conduct research that will enhance our understanding of child health and development. Such cores – such as biorepositories/biobanks, biomolecular core labs, bioinformatics platforms and cell imaging

technologies that provide insight into cell, tissue and organism function— are increasingly cost-prohibitive for single institutions to obtain and, to achieve full impact, require the use of multiple aligned research teams and institutions. Support for the establishment of self-sustaining core infrastructure is needed. We urge that portions of awards be dedicated to support training of early-career basic, translational, and clinical scientists who are committed to pediatric research so that we may develop the future generation of researchers to sustain the impact of ECHO.

Considerations for harmonizing data across cohorts

[Respondent] supports data harmonization to the greatest extent possible to facilitate cross-cohort analytics. In particular, we recommend using existing models such as PEDSnet. PEDSnet is a collaboration of healthcare organizations and disease-specific networks that are working together to form a national pediatric learning health system. PEDSnet benefits from robust resources and a history of collaboration by pediatricians that has reshaped outcomes for previously fatal diseases, such as cystic fibrosis and childhood cancers. PEDSnet is one of the 11 clinical data research networks funded by The Patient-Centered Outcomes Research Institute (PCORI), with a mission of helping people make informed healthcare decisions and improving health delivery and outcomes through the production and promotion of high-integrity, evidence-based information from research guided by patients, caregivers, and the broader healthcare community.

High impact areas of opportunity in addition to those listed

Generally, studies should be oriented toward prevention and recognize that the arc of childhood development encompasses pre-conception, in-utero development, post-natal, childhood and adolescent development, as well as influences of genetics and environmental influences on such development. We strongly encourage that NIH recognize this reality by ensuring this outlook spans the focus areas put forward. We also encourage a focus on the environment and surrounding community/neighborhoods and a strong focus on community engagement. More specifically, birth address data or zip codes should be used to geomap to socioeconomic, built environment, community assets, etc. to more fully inform the field regarding the impact of these factors on health.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

As data collection systems and methodologies are implemented, it is imperative that all of the data should be captured electronically in health information systems in a consistent format. We encourage the use of population health dashboards and harmonization of electronic systems (i.e. PEDSnet). We have an opportunity to prospectively standardize collection of risk factors at a national level throughout health care institutions. This should include measures of health literacy, English proficiency, perceptions of racism, family structure, etc. One specific area that could be addressed is including definitions for diagnoses in order to ensure that clinicians are being consistent. There are instances in which one clinician would code a patient's condition as asthma, whereas another clinician would code the same condition as reactive airways disease. Establishing a common set of definitions would help to avoid variations among what clinicians mean by specific diagnoses.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

Within the identified focus areas, we suggest an orientation around prevention that includes improving

the health of populations through a focus on community involvement and better understanding the impacts of the built environment/addressing upstream determinants of health. Regarding existing research studies/resources, we suggest drawing upon: Asthma – The American Lung Association’s Airways Clinical Research Centers are a model network for conducting large clinical trials dedicated to asthma treatment and often partner with the NIH to co-fund innovative approaches to conducting clinical research studies. Additionally, the Center for Medicare and Medicaid Innovation funded a number of awardees focusing on asthma. For example, Nemours/Alfred I. duPont Hospital for Children’s award focused on the use of a patient-centered medical home, coupled with community integrators and navigators. Obesity – Existing patient and population dashboards should be explored. This includes risk stratification in the primary care setting. Additionally, the Centers for Disease Control and Prevention (CDC) has funded a number of community-based obesity prevention interventions, and the agency should be consulted. CDC’s Guide to Community Preventive Services is a resource for evidence-based Task Force recommendations and findings about what works to improve public health. Neurodevelopment – We suggest inclusion of motor disorders, speech & communication, neurodevelopmental outcomes post anesthesia and post surgery, and brain injury, including developmental encephalopathy due to gestational or early life exposures, in this category. The AAP/ACOG article Neonatal Encephalopathy and Neurologic Outcome, Second Edition bolsters the case for inclusion of the brain injury focus. Premature infants are at risk in several of these areas - The NHLBI PROP (Pediatric Respiratory Outcomes Program) is one cohort, for example, that would provide some maternal information, robust neonatal ICU information, especially regarding respiratory phenotype, and first year of life respiratory outcomes for babies born <29 weeks (n=835 enrolled babies with n=717 survivors with one year follow up).

The additional IDeA States opportunity

[Respondent] strongly supports the IDeA proposal as it strengthens ECHO by providing access to diverse state populations. IDeA states have a proven history of collaboration. The Delaware INBRE has flourished because of strong collaborations with six partners. Through our IDeA CTR award, [Respondent] is partnering with Christiana Care Health System, the University of Delaware and the Medical University of South Carolina to support clinical and translational research. This is a strong foundation to build upon and leverage through an IDeA States Network, allowing institutions in IDeA states to further develop research infrastructure and amplify partnerships to implement clinical trials. This proposal would serve the needs of children and lessen the gap between IDeA states and other states that have traditionally received more federal funds. The Network could build upon cohorts that institutions in IDeA states participate in: • NIH’s Community Oncology Research Program: Nemours’ participation is giving more children access to clinical trials and furthering best practices research in cancer care. • The Delaware Comprehensive Sickle Cell Research Center (funded through COBRE) will undertake clinical trials addressing sickle cell pain/inflammation. • A few IDeA states including Delaware participate in PEDSnet or PCORnet. PEDSnet is focused on Crohn’s Disease and Ulcerative Colitis, Obesity, and Congenital Heart Disease. Pediatric cohorts through PCORnet Patient-Powered Research Networks include Autism, Duchenne Muscular Dystrophy, Nephrotic Syndrome, Childhood Arthritis, Epilepsy, Rare Genetic Diseases, and Immune Deficiency. • Other networks include: Cystic Fibrosis Patient Registry and ALA’s airway clinician research center. As a member of the Coalition for Pediatric Medical Research, we do NOT see this opportunity as a substitute for creation of the National Pediatric Research Network. It would be a complementary proposal to provide resources where they are most needed to assure that all states can meaningfully participate and that the needs of underserved populations in these states are addressed.

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

(Submitter left answer blank)

Considerations for harmonizing data across cohorts

To optimize the feasibility of merging core data elements across studies the investigative teams will need to include statisticians, computer programmers, and data analysts with experience in harmonizing big data. For example, the longstanding tradition of conducting studies at Olmsted County, MN using a large unique population-based birth cohort has created an accumulation of rich data that allows investigators from other research communities to build a new study at little additional cost. In addition, it facilitates and opportunity for synergistic amplification of these data that translate into more rapid and efficient dissemination and implementation of clinically relevant data.

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

Based on our experience we would suggest the following considerations for meeting the ECHO data collection and analytic methodologic requirements. A comprehensive approach to hypothesis driven clinical translational research requires: 1) An experienced well integrated multidisciplinary team consisting of MD/PhD epidemiologists, neurodevelopmental/behavioral pediatrician, psychologist, pediatric intensivist, speech and language pathologist, school education specialists, statisticians (with expertise in handling huge datasets), and data abstractors (with years of experience). In addition, as new specific clinical questions arise, accessibility to a pool of different pediatric and clinical subspecialties (with research background) should be available. 2) A methodologically rigorous epidemiologic scientific approach consisting of: a. Identification and accessibility of every member of the population-based birth cohort, not just those with the disease of interest. b. Defined and validated operationalized research criteria to identify true cases of disease and outcome. This approach will also enhance harmonization of data across studies. c. Complementary data resources (for example medical and school records, and detailed birth certificate data) for every child (with and without disease/exposure of interest) in the cohort to longitudinally evaluate all potential variables with relevance to disease development and outcome. d. Trained and experienced data abstractors as part of the research team. e. Abstraction of data to be done through systematic, multi-staged, multi-resource process allowing accumulation of all required information (e.g. details of symptoms, tests, interventions, comorbidities.....) for every child in the cohort. f. Reliability and validity of abstracted data must be addressed regularly throughout the study. g. Support from biostatisticians, biomedical informatics specialists, and programmers.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

The existing population-based Olmsted County, MN birth-cohort will support large scale, long-term

studies of children, mothers, fathers, siblings to study environmental exposures on child health and development. 1) Every member of the birth-cohort has been identified (n=55,215). All children born 1976-2007 to mothers who were residents of Olmsted County, MN at the child's birth are included. 2) For almost 20-yrs our multi-disciplinary team has successfully characterized some environmental risk factors (e.g. early childhood anesthesia), incidence rates, healthcare utilization, and long term outcomes associated with: intellectual disability, learning disability, Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), and speech/language impairment. 3) The following data resources are available for every child in the birth-cohort: a. Detailed school records (all 41 public/private/home-schooled). Mayo Clinic has a unique research agreement to access the cumulative school records that includes: drop-out, expulsion, , absenteeism, frequency of school changes, graduation status, school achievement tests (group and individual IQ/Achievement Tests), individual education plans, Chapter I/Title I enrollment, neglect/alcohol/drug abuse for mother/father/child, parental education level, and marital status.... b. Rochester Epidemiology Project has collected and linked medical information across all healthcare systems utilized by Olmsted County, MN residents since 1966. Detailed information for every medical encounter across the child's/parents/siblings lifespan is linked through patient-based medical records (outpatient,ER,hospital encounters,psychology/psychiatry/social-service reports,medication, laboratory/radiology/pathology results). c. Detailed birth certificate data (demographics,biological,socioeconomic,risk/protective factors). d. Pre/peri/post-natal exposures can be explored. In summary, comprehensive unparalleled data resources are available to retrospectively and prospectively pursue hypothesis driven investigation of the ECHO Core elements and focus areas. Medical information is also available for fathers/siblings/other family members. Biospecimen collection has been completed for 1,211 children (ongoing ASD and ADHD investigations). Successful prospective recruitment of the birth-cohort for neuropsychiatric testing in our ASD, ADHD, anesthesia exposure studies demonstrate the feasibility of expanding these efforts to support future ECHO initiatives.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

Leveraging existing cohorts is an ideal way to make expedient progress on a variety of child health outcomes; the main advantage being a multi-year and in some cases decades head start in data collection on health outcomes and related mechanisms. The more mature of these existing cohorts may have observations and samples on multiple generations. The opportunity to study such multi-generational cohorts is particularly appealing in the case of diseases that have increased in incidence in recent decades as well as other diseases potentially related to environmental factors, because environmental exposures affect at minimum two generations (the exposed individual and their germ cells that will produce the next generation). Cohorts including grandparents, parents, and children can determine whether the health outcome-specific epigenetic transmission or the transmission of behavioral traits in two consecutive generations are acquired during intra-uterine exposure or, alternatively, are due to grandparental settings. A potential disadvantage to utilizing existing cohorts is the potential lack of information or samples to ideally address a specific question. However, there is in many cases an opportunity to supplement missing elements from existing cohorts. For example, blood

spots on Guthrie cards, which are collected by all and banked by some state public health departments, can be used to obtain genetic, epigenetic and environmental exposure data. Thus, it may take less effort, time and resources to collect missing data on an existing cohort than to establish a new cohort. There are a variety of established cohorts that have provided exceedingly valuable information on environmental influences on child health outcomes. A number of these cohorts are located outside of the U.S. and yet have tremendous relevance to health outcomes of the U.S. population. Including relevant non-U.S. cohorts in these research efforts will further accelerate the understanding of environmental influences on child health outcomes.

Additional core elements to be considered

We suggest that pregnancy conditions and environmental exposures during the prenatal period are critical to child health outcomes and as such should be an explicit Core Element. Particularly, information about pregnancy conditions will allow the identification of ways to interrupt the transmission of parental risks to the next generation. The interaction of genetic, environmental, epigenetic data, and gene expression during pregnancy and in neonates can be used to identify children who are at a higher risk and allocate them to proven success treatment regimes (precision medicine applied in a public health setting). For instance as relates to allergy, we can use gene expression data to identify infants at high risk of atopic dermatitis, who would largely benefit from treatment re-establishing a functional skin barrier, which in turn should prevent the 'allergic march' towards asthma. In order to use of results of cohort studies to improve public health, we believe that it is essential, to include small projects (R21) that can quickly respond to such findings and test its proof-of-concept. (The current process in NIH takes too much time.) Hence, we believe that next steps also should involve funding to test whether we can interrupt the transmission of diseases and smoking from mother to child. We do not anticipate that it is possible to develop clinical or preventive trials but to conduct proof-of-concept studies in smaller samples. Examples of such proof-of-concept studies could include determining: 1) If smoking cessation during pregnancy interrupts the transmission of the desire for cigarettes, which can, e.g., be tested using DNA methylation or gene expression in cord blood (AHRR gene); and 2) If improved treatment of maternal allergy or asthma during pregnancy reduces epigenetic marks or related gene expression so that the offspring generation is less biased to develop allergies and asthma (IL1RL1 gene).

Considerations for harmonizing data across cohorts

We also appreciate the idea to harmonize data collection and analyze data with the help of a Coordinating Center. We believe that the collaboration of multiple groups and multiple ideas instead of competitive disputes will provide the necessary gain for better understanding in the complex area of environment, genetics, early epigenetic markers, and various child health outcomes. In addition, our experience has shown that collaboration with other cohort studies provide the necessary opportunity to replicate findings of a single cohort in other groups.

High impact areas of opportunity in addition to those listed

We agree with the four Focus Areas. In addition, immune processes are closely related to all focus areas (respiratory health, obesity, neonatal outcomes, neurodevelopment). Thus we suggest the explicit inclusion of immune processes as an additional focus area. Immune processes and related epigenetic effects are relatively easy to determine during pregnancy and in cord blood and will aid the development of better prediction models. Immune processes and related epigenetic changes are also related to vaccinations, in a positive way. For example, our preliminary data suggest that Tetanus vaccination is associated with changes in methylation of specific nucleotide sequences (CpG sites), which in turn reduces the risk of asthma in children. Additionally, we suggest including eczema (atopic

dermatitis) as a focus area together with upper and lower airway diseases. Eczema typically starts in infancy. It is estimated that up to 30% of all children are affected by eczema, which in turn is related to an 11 times higher risk of peanut allergy and a higher risk of asthma, both can be life-threatening. Eczema is related to excessive scratching in infants leading to discomfort and disrupting their sleep. Eczema in infancy often is the starting point of what is known as 'allergic march,' a series of allergic manifestations often culminating in asthma. Eczema is associated with the combined effects of genes and environment, including gestational conditions, which can result in a disturbance of skin barrier function and relapsing inflammation. We have demonstrated that epigenetic change in cord blood are of importance. We believe that it is important to identify mechanisms, and not to focus on co-occurrences of exposures and diseases.

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

One grain of salt of an overly ambitious "implementation of state-of-the-art data collection and analytic methodologies" is the risk that this becomes an administrative task to establish one norm, not a scientific approach to harmonize. Harmonization should allow deviations to create novel and innovative approaches. Regarding state-of-the-art analytic methodologies, it is important to include creative biostatisticians, who can test multiple appropriate approaches, but not an administrative institution, that unifies analytic methodologies to the smallest denominator. The harmonization should also include collaboration with other birth cohort studies in Europe and Australia.

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

Existing research studies that are of particular interest is the British three-generational Isle of Wight birth cohort study with 1,436 participants, which provides a unique opportunity to link exposure, genetics, and epigenetics over three generation (F0, F1, and F2). The study collected multiple biological samples (blood, placentas, and urine from birth to age 18), conducted allergic sensitization tests, and followed 90% of the population through age 18 years. The Isle of Wight birth cohort addresses airway diseases (asthma, wheezing, and lung function), development of obesity from age 1 to 18 years in F1, and in F2 in early infancy. Regarding exposures, the focus is on pregnancy, normal indoor and outdoor exposures, and specific conditions (e.g., pets, vaccinations, oral contraceptive use, and smoking initiation). Multiple publications have shown the role of gestational and early life exposures in this cohort. This cohort has the scientific team working at the forefront of biostatistical approaches of epigenetic analyses and of epidemiologic model to understand the trajectories of respiratory disease and allergies and of obesity in childhood and adolescence. The Kaiser Permanente in California has a similar data over three generation as does the Michigan Fisheater Family study with foci on neurodevelopmental disorders and endocrine disruptions. In addition, we also like to emphasize the scientific value of birth cohorts with specific foci. For instance, cohort data collected after the Chernobyl accident in the Ukraine and the Michigan Fisheater study (three generations) offer unique chances to address health effects resulting from ionizing radiation and from exposure to PCBs and DDE, respectively.

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

see attachment

Additional core elements to be considered

see attachment

Considerations for harmonizing data across cohorts

see attachment

High impact areas of opportunity in addition to those listed

see attachment

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

see attachment

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

see attachment

The additional IDeA States opportunity

see attachment

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

(Submitter left answer blank)

Additional core elements to be considered

In regard to the proposed plan for the Environmental influences on Child Health Outcomes (ECHO) program, there appears to be no focus on paternal factors (e.g., chemical, social, physical) or the mechanisms by which they may impact offspring health and development (e.g., sperm epigenetics). A growing body of compelling data in animal models demonstrates that environmental factors encountered by the adult male can be embodied within the developing germ cell (e.g.,

spermatogenesis). In turn, these epigenetic marks can impart information at fertilization that affects the trajectory of offspring health and development. For example, nutritional manipulation, such as pre-diabetic conditions, in adult male animals resulted in epigenetic dysregulation of sperm, which subsequently conferred metabolic disorders in offspring (Wei et al 2014: PMID: 24449870). In this context, pre-conception paternal environmental factors are an important component of offspring health – and are burgeoning aspect of Developmental Origins of Health and Disease (DOHaD) hypothesis. In order to capture the full breadth of factors that influence offspring health, paternal environmental contributions should be considered as one of the focuses in the Core Element, “Epigenetic influences on early childhood development”. Although most of the existing data for the role of sperm epigenetics and offspring health and development are limited to animal studies, such research in humans is already underway including ours (1K22-ES023085-01 ; PI: Pilsner, JR). Thus, ECHO should leverage existing cohorts to expand research focus to include paternal environmental exposures and sperm epigenetics.

Considerations for harmonizing data across cohorts

(Submitter left answer blank)

High impact areas of opportunity in addition to those listed

(Submitter left answer blank)

Anticipated advances and/or considerations for implementing state-of-the-art data collection and analytic methodologies throughout the duration of the study

(Submitter left answer blank)

The four Focus Areas:

Suggestions of existing research studies or resources that might address one or more of these areas, including a description of the study or resource (e.g., sample size, demographic information, major health or behavioral outcomes, environmental exposures, success with or potential for follow-up through childhood, available biologic or environmental specimens)

(Submitter left answer blank)

The additional IDeA States opportunity

(Submitter left answer blank)

The Core Elements:

Potential benefits, drawbacks, and areas of consideration for leveraging existing cohorts to collect standardized data elements

There is great potential for pooling/merging existing cohorts. However, decisions about which studies should be funded under the ECHO program will need to be based on criteria that go far beyond the standard set of reviewer criteria. There is no doubt that the scientific quality of the applicant studies must be of the highest caliber. But beyond that, if the true objective of ECHO is to create a "super study" that will be far more informative than the individual studies alone, study elements such as current/past data collection instruments, biological sample collection, physical exam information and timing of data collection must be carefully evaluated for the potential "combinability" of the studies. This evaluation is especially important for data that was collected during the pre/post-natal and early childhood periods that cannot be reconstructed. Studies would not have the potential to be merged together in an

informative way if their existing data are so disparate that they are incompatible; the objective of ECHO will be obscured. Studies applying to be part of ECHO should be required to provide their questionnaires and other data collection instruments

The following RFI responses were submitted as attachments through the web-based portal.²

[Respondent] has been part of ... since 2008. The Center's goal is promote, protect, and preserve the health of children and adolescents through education in environmental pediatrics, research and medical consulting services. The CEH has worked in collaboration with ... providing consultations and educational outreach to healthcare professionals, public health officials, policy-makers and community organizations. ... seeks to increasing knowledge about children's environmental exposures among the public and healthcare professionals. [Respondent] provides health education activities tailored to meet the needs of the various target populations. The activities include: grand rounds presentations, community presentations, continuing medical education sessions and fact sheet development. The fact sheets developed over the past year in Puerto Rico include topics: pesticides, carbon monoxide, and asthma fact sheets. In June 2009, [respondent] successfully collaborated with ... to sponsor the first Puerto Rico Children's Environmental Health (PCEH) conference. The 2nd PCEH Conference, held on April 14, 2012, focused on prenatal and neonatal exposures; Maternal and Child Health and the Environment. [Respondent] led a Children's Environmental Health Symposium on March 20, 2013 in San Juan. The title of the session was "Translating Science to Action: What You Need to Know About Environmental Exposures in Babies, Toddlers and Teens." [Respondent has] developed a fellowship that provides advanced training in pediatric environmental health. The program's goal is to produce future research leaders in the emerging field of pediatric environmental health.

To Whom It May Concern:

[Respondent is] pleased to describe the capacity ... that could support a potential Coordinating Center for the Environmental Influences on Child Health Outcomes (ECHO) Program (The National Children's Study Alternative) in collaboration with ...

[Respondent] is committed to optimizing the research infrastructure that supports clinical and translational research ... The working "units" ... currently comprise an integrated network of components and programs. These resources are organized to optimize success in achieving our five strategic priorities: 1) enhancing the research infrastructure; 2) promoting investigator education, training and career development; 3) accelerating discovery across the T1 interface; 4) building community partnerships; and 5) expanding value-added partnerships. All the resources ... can be accessed through a system of senior staff guides and a web-based access portal ...

In the revised application ... for our second cycle of funding, we have significantly strengthen our ties with ... through the addition of seven faculty to serve as co-leads of several modules including: Collaboration and Multi-disciplinary Team Science; Community Engagement; Biostatistics, Epidemiology, and Research Design; Integrating Special Populations; Participant and Clinical Interactions; Liaison to Recruitment Innovation Centers; and Evaluation and Continuous Improvement.

Through these enhanced collaborative interactions, [respondent] can readily deploy our unique resources in support of a Coordinating Center proposal to provide administrative, methodological and analytical support for the ECHO Program.

² Identifying information has been removed

[Respondent] appreciates the opportunity to respond to this RFI describing the NIH ECHO program. Children's environmental health (CEH) is a priority of the [respondent]. Our response to this RFI is in the context of ... [publication]. [Respondent] priorities are for research focused on understanding impacts from complex, real-world exposures to air, water, and manufactured chemicals; and for translated science to evaluate alternative actions and to predict outcomes.

[Respondent] applauds this NIH effort to leverage existing cohorts in a way that will build the evidence base for action to prevent disease. The four health outcomes that NIH has selected align with the four outcomes that [respondent] has identified: birth outcomes, metabolic syndrome, neurodevelopmental disorders, and asthma.

[Respondent] stressed the importance of measuring early indicators and understanding common origins of these diseases including endocrine disruption. [Respondent] also emphasizes that strong proposals should incorporate advanced exposure methods to characterized modifiable exogenous environmental factors; to include multiplexed and untargeted measurements. To this end, [respondent] suggests that an important core element be added: "early markers of effect." Strong proposals will examine potential interaction and impact of multiple stressors on disease etiology, including understanding of impacts of environmental exposures on related intermediate endpoints ("origins"). Ideally, investigators will postulate adverse outcome pathways (AOPs) and AOP networks based on genetic risk factors for the disease outcome of focus and include appropriate measures in the study design.

Finally, [respondent] believes that strategic collaboration with, and leveraging of, associated research that applies experimental models of disease to explore and confirm mechanisms as well as gene-environment interactions will better inform CEH intervention and public health policy. A key goal of the [respondent] is to foster collaboration with federal partners to address... science needs. We see potentially high impact opportunities to leverage extant cohorts of EPA STAR grantees under ECHO. We look forward to working with NIH to meet common goals for science to support CEH.

We applaud the NIH's interest in establishing a large, collaborative study of children's health, focusing on epigenetic influences and environmental factors on airway disease, obesity and metabolic disorders, neurodevelopment and other outcomes. We would like to raise five points. First, we note that many of the existing cohorts have existing biospecimen banks that afford further analyses of "new" biomarkers but others may not have extant biological samples from early life available for study. Nevertheless, all of these cohorts are invaluable for validating outcome measures and for piloting new methods of data collection, e.g. rectal and buccal swabs for microbiome studies, evaluation of pubertal timing, and evaluation of data collection methods to capture early pregnancy. Second, the psychosocial environment is a prevailing theme across all focus areas and we would emphasize the measurement of multiple dimensions of social circumstances, including objective (parental education, occupation and income) and perceived measures. Third, we suggest that emphasis be placed on the built environment as this is likely important for the focus areas as well. Fourth, as many of the outcomes in the focus areas may result from an interaction between measures of cumulative stress, e.g. allostatic load, with other factors, especially environmental contaminants, we suggest that emphasis be put on measurement of factors related to cumulative stress, e.g. biomarkers associated with allostatic load and telomere length and that these should be included in the common protocol. Finally, common protocols should, to the extent possible, be developed; however, many of the existing cohorts already have protocols in place,

and sufficient attention must be given to data harmonization. In summary, we strongly support the NIH endeavor and emphasize the importance of attention to accurate measurement of environmental exposures, aspects of social circumstances, the built environment, and stress measures as well as validation and data harmonization.

Dear NIH Officials,

Thank you for the opportunity for [respondent name] to respond to the RFI requesting input on the Environmental Influences on Child Health Outcomes (ECHO) Program. [Respondent] is the coalition involving approximately 150 scholarly basic scientists, clinicians, social sciences, patient groups, etc. totaling two million individuals, concerned with solving problems of drug abuse and addiction. We see many redundancies between the Core Elements listed in the RFI and the objectives of the Adolescent Behavioral Cognition Development (ABCD) Study which has been initiated by the National Institute on Drug Abuse and other NIH Institutes. Therefore, we request that serious consideration be given to our recommendation that the use of funds available from the ECHO study be allocated to support the ABCD study. In this way the goals of both studies will be achieved without duplicate funding. Both studies have recognized the importance of demographics, environmental factors, and generic influences on the development of youth. It is highly expected, but not definitively documented that neonatal and adolescent exposure to chemicals such as those that are abused by all socioeconomic, geographic and ethnic sectors of society is a cause for future deficits in development. The major objective of the ABCD study is to clearly elucidate the effects of these chemicals on the neurodevelopment of adolescents, clearly a major objective of the ECHO initiative. The serious deleterious consequences, especially the recent rise in the number of deaths of children, adolescents, parents and others are a major reason for additional efforts to increase our understanding of how these drugs affect all aspects of childhood development.

Dear National Institute of Health,

I am reaching out to you from ... about the NIH decision to repurpose funds that were originally slated for the National Children's Study (NCS). Currently, there is no money designated under ECHO for research on the impact of climate change on child health.

Our organization is an international coalition of hospitals and health care systems, medical professionals, community groups, health-affected constituencies, labor unions, environmental and environmental health organizations and religious groups and we urge you to reconsider this very important funding issue.

Climate change is the most important environmental health problem confronting society. We believe that some of the funds from the ECHO program should be used to support research related to the impact of climate change on children's health. Such research might look at the impact of climate change on pregnancy and the outcomes of pregnancy, the impact of climate change on developmental and behavioral outcomes, the impact of climate change on childhood nutrition, the impact of climate change on pulmonary disease (asthma and other problems), the impact of climate change on childhood infections and a number of other issues. Much of this research could be undertaken using existing or newly developed cohorts.

As you know, climate change poses one of the single largest threats to public health and children are one of the groups most at risk from these impacts. We understand that NIH funding is limited, but we urge you to prioritize funding to support research to better understand the impact of climate change on children's health.

To: Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director, NIH

Re: Request for Information (RFI): Inviting Comments and Suggestions on the Environmental influences on Child Health Outcomes (ECHO) Program (the National Children's Study Alternative) (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-117.html#sthash.PRFygkCC.dpuf>)

We believe that some of the funds from the ECHO program should be used to support research related to the impacts of climate change on children's health, including the co-benefits of mitigation. Much of this research could be undertaken using existing or newly developed cohorts. For example, the Columbia Center for Children's Environmental Health, funded since 1998 as a national Center by NIEHS and EPA, has enrolled and is continuing to follow a cohort of inner city African American and Dominican children since the mother's pregnancy through adolescence. By documenting the co-benefits of reducing air toxics from fossil fuel combustion, this work has provided, and will continue to provide, impetus for action on climate change. We have found evidence high prenatal exposure to polycyclic aromatic hydrocarbons/PAH (released by diesel and gasoline powered vehicles, residential oil burning, and power generation by coal or natural gas) is associated with adverse birth outcomes, developmental delay, reduced full scale and verbal IQ, loss of white matter in the brain, symptoms of anxiety and depression and ADHD, as well as higher odds of wheeze and asthma at age 5-6, increased risk of allergic sensitization, and obesity in childhood. In addition, the CCCEH has enrolled younger siblings of cohort children and has resumed enrolling children into the current cohort, providing an extensive bio-specimen bank and a rich dataset from children enrolled from 1998 through the present and beyond. In addition to co-benefits of reducing fossil fuel burning, these resources afford the opportunity to document the link between area-wide climate related changes such as higher temperature and increased aeroallergen concentrations on the health of children. This work has been carried out in partnership with WE ACT, and other community and environmental justice organizations in New York City.

Compared to term-born infants, preterm infants have higher rates of childhood and adult respiratory morbidities, including asthma, neurodevelopmental problems, including autism, ADHD, and social/behavior problems, growth failure and paradoxically increased risks for metabolic syndrome and hypertension. Inclusion of one or more existing preterm cohorts represents a high impact area of opportunity not specially mentioned in the ECHO RFI.

One such existing cohort is the NHLBI-supported Prematurity and Respiratory Outcomes Program (PROP), a prospective cohort study of 835 preterm infants born <29 weeks gestation recruited from 13 tertiary NICUs. Among the 722 survivors to 1-year, 95% completed the 12-month follow-up. The extensive PROP database includes maternal and infant demographics, daily infant respiratory, growth, nutritional, and medication data throughout the NICU stay, family history of atopy and asthma, and validated post-discharge questionnaires to assess respiratory morbidity and medication use at 3, 6, 9

and 12-months corrected age, and a survey of environmental respiratory irritant exposures. DNA from participants and parents were collected. There are >12,000 aliquots of urine in the PROP biorepository representing samples collected twice in the first week of life and at 2 and 4 weeks of age. Families were consented for continued contact after 1-year in anticipation for longer-term studies. In a subset of approximately 110 participants at 12-18 months infant lung function tests were performed, the largest study of physiologic respiratory outcomes in a preterm population.

This cohort represents a unique opportunity to explore the intersect of health outcomes, such as asthma, atopy, growth and neurodevelopmental status with maternal environmental exposures temporally associated with preterm birth, (e.g. urinary cotinine, lead and pesticides), environmental exposures in the NICU (drug metabolites, phthalates, bisphenol A) and genomic data. Urinary metabolomics provides opportunities to link early life dietary and toxic exposures, metabolism and health outcomes in this vulnerable population.

This is a response to RFI NOT-OD-15-117 "Inviting Comments and Suggestions on the Environmental influences on Child Health Outcomes (ECHO) Program".

The stated priorities of the ECHO initiative include prevention of upper and lower airway disease in children, and the support of ongoing birth cohorts. We are therefore requesting that future funding opportunities based on ECHO include mechanisms to support a collaboration involving the US birth cohorts that focus on allergy and asthma as outcomes.

In September 2012, several NIH institutes sponsored a workshop for allergy and asthma birth cohorts in an effort to identify research priorities and foster collaboration. There were several tangible results of this effort, including a website listing the major cohorts, study population and overall study design with sampling strategy (AsthmaBirthCohorts.niaid.nih.gov). This workshop also led to a joint publication that listed major questions, suggested initiatives, and outlined steps for collaboration.¹ One major obstacle at the time was the lack of a funding mechanism for a large collaborative effort among US birth cohorts.

The ECHO initiative provides an outstanding opportunity for collaborative research, and has spurred conversations among cohort leaders who are willing to combine data sets to construct a national birth cohort consortium, and to formulate potential goals, objectives, and structure for this multicenter project. The leaders of cohorts in Boston, Cincinnati, Detroit, Madison, New York and Tucson (see Table) have expressed enthusiasm and commitment towards building a consortium. These investigators represent all of the non-interventional birth cohorts listed on the NIH Birth Cohort website that a) focus on asthma and allergy outcomes, and b) initiated data collection at or before birth.

Goals, aims and hypotheses for the consortium are still being developed, but will include the development of a central data storage repository that will be accessible to all of the participating investigators. Further, we will advance the field not only by combining our data sets, but also by sharing expertise and learning from each other through networking and frequent contact. First steps will include data harmonization and building the collective data set. Next, the initial objective will be to define asthma endotypes, defined as subtypes of childhood asthma with shared biologic characteristics. This is an essential first step in studying the complex disorder of childhood asthma, and will allow large-scale studies of endotypes that are clinically important (e.g. early multiple sensitization) and yet represent

only a small portion of the participants of each individual birth cohort. Currently, individual cohorts are underpowered to accurately define asthma endotypes, and to identify associated biomarkers, risk factors, and mechanisms. Development of a consortium with a large sample size, representation from multiple races and ethnicities, and advanced analytics could overcome these issues and provide new opportunities for collaborative projects. In addition, the asthma and atopy endotypes defined from pooled data would improve the quality of outcomes for mechanistic studies that utilize specialized data from one or more cohorts.

To achieve these goals, the structure of the consortium would include the following elements:

1. Expertise for data harmonization and construction of a central database. This would require data managers with graduate-level experience in programming to be funded at each site to prepare data and metadata for uploading into the central server.
2. Data storage hardware, and adaptation of Asthma e-Lab software that will be provided by the European STELAR consortium.² A Program Manager with expertise in software engineering would be needed to adapt existing software, oversee the central database, and coordinate data uploads from each cohort.
3. Administrative support to include funding of training sessions for data managers, webinars for investigators, and periodic meetings for an External Advisory Committee and Steering Committees.
4. A data coordinating center to provide state-of-the-art analytics including machine learning techniques and advanced techniques for pattern recognition and statistical analysis.

We would welcome further conversations with NIH staff about our proposal and potential opportunities and mechanisms for funding through the ECHO initiative.

We suggest that the NIH ECHO committee consider the Conditions Affecting Neurocognitive Development and Learning in Early Life (CANDLE) study to address an important gap in understanding how environmental exposures affect U.S. child health. Our approach to studying environmental exposure uses the public health exposome (PHE), an exposure science approach towards characterizing the eco-exposome and the biological and cumulative pathways. Using the PHE framework and a novel systems approach, CANDLE is well established to explore how in utero and early post-natal chemical and non-chemical exposures set the stage for altered child development. Specifically, we suggest the future RFA include how to operationalize chemical (metals; free radicals associated with PM_{2.5}) and non-chemical (natural, built and social environment) interact with various omics to affect development and health in early childhood. The CANDLE study enrolled a sample of 1503 pregnant women from Shelby County, Tennessee in 2006 who reflect the county's demographics: primarily African American (68%) and Caucasian (32%) with notable socioeconomic diversity at the individual and neighborhood level. Mothers and their children have participated in clinic, home and phone assessments from throughout pregnancy and then annually through age 4 of the child, with strong retention rates (range 75-88.5% per exam) Assessments include objective and subjective measures of mother and child include neurocognitive, nutritional, psychosocial and physical health. Stored biological samples include maternal blood and urine during pregnancy; offspring cord blood and placental tissue; maternal, paternal and offspring buccal cells; and child blood and hair. Geo-coding and linking residential histories of study participants to environmental databases are in place. We believe this cohort provides a unique opportunity to rigorously examine environmental influences on child health outcomes in an understudied region of the U.S. CANDLE includes a multidisciplinary team of experts in nutrition, population science, pediatrics, epidemiology, child psychology, biostatistics, and environmental science.

Dear Dr. Tabak:

On behalf of [respondent], thank you for the opportunity to comment on the Environmental influences on Child Health Outcomes (ECHO) program. [Respondent] applauds the creation of this new program to support investigation into environmental influences on child health and development and we are pleased to be a part of the process to develop this important program. We have the following recommendations on the ECHO RFI NOT-OD-15- 117: [Respondent] strongly encourages the cataloging and public availability of previous NIH cohorts that could be considered by investigators for study and to enhance collaboration. Longitudinal cohorts are expensive and some have become dormant due to loss of funding yet contain a wealth of data, information and samples that could be further explored or activated with recruitment of siblings or children from mothers enrolled during pregnancy.

1. We urge inclusion of sleep health as this area in pediatrics touches all 4 of the key pediatric outcome areas.
2. We encourage the aggregation and harmonization of data from common theme longitudinal cohorts, such as asthma, lung growth and functional development to enhance insights into environmental elements including outdoor and indoor pollution including biomass pollution with a large data set.
3. We support the development and inclusion of genomic, epigenetic, proteomic, metabolomics, and biomarker signature identification to further our understanding of interactions with environmental exposure on key datasets.
4. We urge consideration of the inclusion of other critical populations of children in addition to urban and rural populations through IDeA as many children reside at altitude, which is an environmental exposure that can impact the key focus areas.
5. We encourage investigation to evaluate the impact on families, socioeconomics and health care expenditures related to environmental exposures.
6. We encourage the inclusion of investigation to evaluate the impacts of climate change on child health and development.
7. [Respondent] urges the institute to provide further clarification and broad access to “tools” developed through the redistribution of FY15 funds.

We thank the institute for this opportunity to comment on the ECHO program.

Dear Dr. Tabak:

[Respondent] welcomes the opportunity to comment on the NIH Environment influences on Child Health Outcomes Program. We look forward to working with NIH on this initiative. We suggest four issues for NIH consideration as it develops its plan:

Improve pediatric reference intervals: As part of its efforts, NIH should focus on improving pediatric reference intervals. Nearly all future studies that emerge from this project will rely on these data points to define disorders in the pediatric population.

Consider pre-analytic issues: Analytical results are heavily influenced by pre-analytical factors. Collection, transport and storage practices need to be standardized to ensure the integrity of the specimens and the laboratory test values used to make decisions about the studies. Furthermore, new technologies are emerging that allow reasonable point-of-care or field analysis that may suit the needs of these studies. We suggest that NIH work closely with laboratory professionals who are well versed on these issues.

Consult with laboratory experts: The need to collaborate with laboratory specialists in the field of pediatric, maternal and fetal disorders is critical. The knowledge required to differentiate disease entities affected by environmental factors from confounding metabolic/genetic conditions is substantial. NIH should consult laboratory professionals on these matters.

Ensure the harmonization of clinical laboratory results: NIH is proposing a series of longitudinal studies that will collect data from many different research institutions and laboratories. The agency should ensure that the laboratory instruments or methods utilized by research facilities provide 'harmonized' test results so that researchers can make accurate, evidence-based recommendations.

[Respondent] strongly recommends the inclusion of parental occupation as a core element in the Environmental influences on Child Health Outcomes (ECHO) Program, and that occupation be listed under environmental factors. Epidemiologic research suggests parental occupation can contribute to adverse child health outcomes, yet is often overlooked in studies of children's health. Work is an important determinant of parents' health, and occupation during pregnancy can be a significant predictor of pregnancy outcomes. As of 2011, 71.1% of women of reproductive age were in the labor force, and 55% of children were born to working mothers¹. Parental occupation has been associated with various long-term adverse health outcomes in children²⁻⁶. Occupational exposures may affect reproductive and child health outcomes through several potential mechanisms, including⁷⁻¹¹: 1) direct maternal exposures before or during pregnancy that cross the placenta; 2) transfer of paternal exposures to the mother or fetus in semen; 3) transfer of workplace exposures to infants in breast milk; 4) germ cell damage during spermatogenesis; 5) in utero exposure or epigenetic changes to either parent's germ cells from occupational exposures; and 6) contamination of the home environment from chemicals carried on parents' or other family members' clothes, shoes, hair, and skin. Information on parental occupation is easily collected, and existing tools simplify job and exposure coding. Research has demonstrated that simple, open-text questions about type of employer/business and job title/duties can be quickly completed with >95% response rates^{12,13}. [Respondent] developed a free, public, and validated autocoding system... to translate open-text responses to Census Occupation Codes for easy analysis. Tools to map these codes to the North American Industry Classification System (NAICS) and Standard Occupational Classification (SOC) codes are also provided, to facilitate easy linkage to exposure information in O*Net and various job-exposure matrices.

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We applaud the decision to re-direct funds to extant cohorts as a far more efficient and innovative approach, leveraging existing infrastructure, data and biological samples, and allowing for broader investigator input. As challenges exist in pooling data, it is important to ensure inclusion of cohorts with experience measuring environmental factors. Further, it will be necessary to include varying exposures and exposure assessment approaches between cohorts and over time as well as permit accrual of additional first pregnancies into established, ongoing cohorts with the potential for synchronizing selected protocols on a subset of children. Aside from listed priorities areas, immune-related outcomes, including on non-respiratory related allergies and childhood infections are major sources of morbidity in children likely impacted by environmental factors. In keeping with the vision of the US NCS, the IDeA

States National Pediatric Network should prioritize translation of knowledge regarding environmental health hazards in children and cohorts should be limited to US children.

While incorporating foreign cohorts may shed light on shared etiologies of childhood illnesses:

- Regulatory requirements for contaminants in products, food and water vary by country; thus the type, nature and amount of environmental contaminants in the US may not be reflected elsewhere.
- Social/behavioral contexts in which environmental factors occur can differ considerably and there is growing evidence that these factors modify the impacts of environmental contaminants.
- Geographic influences, e.g., on diet/nutrient content of foods and the health care environment could bring generalizability of foreign studies to US children into question.
- Foreign cohorts would not represent the racial/ethnic distribution of US children, e.g., indigenous populations, African Americans. Including IDeA states will strengthen the representation of the cohorts across the US.
- Targeted efforts to establish birth cohorts provided by foreign agencies usually exclude funding of US cohorts. Maintaining the NCS re-direct initiative for US children is paramount.

[Respondent], a national marketing and clinical research data collection company, would recommend the NIH's use of companies such as ours for field data collection and panel management in partnership with an academic institution focusing on the science for the ECHO. By partnering together we are uniquely positioned to support the NIH 2016 plan for ECHO's goal of investigating the impact of environmental exposures on children. Below are some examples of how an experienced field data collection company would be able to support the ECHO.

- A national marketing/clinical research company already has the experience and success of field data collection and participant panel management, working as true consultative partners.
- They will be able to grow or supplement existing cohort's panels by leveraging a diverse and scalable participant panel that includes detailed personal profiles on its members. For example, [respondent] has... opt in participants ready for immediate access to a representative cross-section of the U.S. population.
- Documented experience in recruitment and management of large scale research projects...
- Experience with alternate research methodologies, allowing for rich qualitative and/or quantitative data collection that complements in-person methods. These include the use of webcams, online communities, mobile devices, online surveys and emerging multi-mode options.
- Marketing/Clinical Research Companies who have supported these types of studies will have the infrastructure, knowledge, experience, and leadership already in place to "hit the ground running" from day one.

Thank you for the opportunity to submit a response.

The All Children's Hospital-Johns Hopkins Medicine Prospective Research on Early Determinants of Illness and Children's health Trajectories Study ("PREDICT Study") was launched at All Children's

Hospital-Johns Hopkins Medicine (ACH-JHM) in St. Petersburg, Florida in January 2015. It is, to our knowledge, the first institution-wide prospective inception cohort study and associated biorepository focused on healthy children in a clinical setting.

PREDICT seeks to provide critical insight into effective population- and individual-level disease prevention strategies by collecting data necessary to describe the timing and nature of pre- and post-natal factors that are associated with key pediatric health outcomes including poor birth outcomes, obesity, and developmental delay. PREDICT has two sub-cohorts: A birth sub-cohort that enrolls pregnant women at 12+ weeks gestation, and an early childhood sub-cohort of children from birth to <6 years. Pregnant women and children are followed prospectively in a primary care setting (OB care and pediatrics), which provides medical records for participants. In addition, very detailed assessments of social and physical environments (e.g., individual, family, neighborhood levels) over time are also collected.

PREDICT is an effective protocol for recruiting a birth cohort and an early childhood cohort. It has demonstrated significant success in recruiting participants in its first year. Yet because the cohort is early in the data collection process, it is also well-positioned for addition of new measures and harmonization of measures with other sites. The robust and comprehensive nature of the data collected in PREDICT--ranging from biospecimens to measures of children's social and physical environmental exposures and clinical outcomes--makes it ideally suited to investigating multiple health outcomes prioritized by ECHO. A priori, it is designed with birth outcomes, obesity, and neurodevelopment in mind. But it could also offer opportunities to augment data from other sites investigating upper and lower respiratory diseases, particularly because of the rich combination of data regarding toxic exposures and clinical outcomes that can be gleaned from the biorepository specimens and clinical outcome data respectively.

PREDICT is unique and ground-breaking because it is designed to comprehensively investigate the molecular intermediaries that link proximal signals such as DNA ("risk") and proteomic and metabolomic down-stream signals ("effects") with clinical phenotypes of interest (i.e., birth outcomes, obesity and developmental delay).

PREDICT takes advantage of ACH-JHM's extraordinary investments in the next generation of pediatric research, including research cores in proteomics, and metabolomics, as well as one of the most advanced research biorepositories in the country. Critically, PREDICT has been designed from its inception to collect, prepare, and store biosamples to fully leverage their use with these techniques.

Not only is PREDICT unique in its design for investigating proteomic and metabolomic pathways, but this data collection occurs alongside rich and robust characterization of children's social and physical environments, the exposures upon which disease risk or resilience may ultimately depend. Because of the comprehensive nature of the study design, its inclusion of robust measures of the social and physical environment, and its sophisticated and systematic protocol for collecting biospecimens, PREDICT is well-positioned to yield important findings about the links between social and physical environmental exposures and disease risk, including information on the intermediary biological pathways that contribute to risk.

The descriptions below expand on the limited amount of information we communicated regarding existing research studies or resources that might address one or more of the four focus areas.

ASTHMA: We have several innovative cohorts focused on childhood asthma that integrate genetic and environmental exposure data with longitudinal health outcomes.

1. Greater Cincinnati Pediatric Clinic Repository (GCPCR)

The purpose of the Greater Cincinnati Pediatric Clinic Cohort (GCPCR) is to link and efficiently utilize clinical and epidemiologic data and biospecimens in order to delineate phenotypes of asthma and other allergic disorders (*Pediatr Allergy Immunol Pulmonol* 2012; 25:104-113). Children are invited to participate in the GCPCR upon presentation to a CCHMC clinic or ED. Following informed consent, questionnaires are administered regarding asthma and respiratory symptoms, allergy and skin symptoms, personal and family medical history, environmental exposures, medication adherence and demographics including age, gender, race, ethnicity, household income, parental education and insurance payment method. In addition, all subjects with allergic disease fill out the Pediatric Allergic Disease Quality of Life Questionnaire, and subjects with asthma complete the Asthma Control Test. Clinical data including physical exam findings, physician diagnoses, weight and height, results of allergy skin prick tests (SPTs), pulmonary function tests (PFT), chest and sinus x-rays, and other clinical and laboratory tests are extracted from the subjects' electronic medical records. At the time of recruitment, patients also are asked to provide a DNA sample. Nearly 7,000 participants have been enrolled including 2,406 with asthma, 3,994 with an allergic disease or disorder and 249 non-asthmatic, non-allergic controls. DNA samples from over 1,700 participants have been genotyped. This repository is a rich resource and serves as the basis of several projects and recruitment for clinical research studies. It is funded by the NIAID U19 Asthma and Allergic Diseases Cooperative Research Center (PI - Dr. Khurana Hershey).

2. Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) birth cohort

The Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) is a birth cohort of 762 children born to at least one parent with a positive skin test to an aeroallergen and current allergy or asthma symptoms, which is funded by the NIEHS. Children were identified from birth records in the Greater Cincinnati Area between 2001 and 2003. Levels of exposure to traffic related particulate matter, was determined by land use regression for each address the child regularly spent time including home, daycare, babysitter etc. to determine objective quantitative estimates of traffic related exposure. Dust samples were collected from the child's primary activity room before the first research exam (~7 months of age) and analyzed for allergens including dust, cat, dog, cockroach, and mold, as well as endotoxin and beta-glucan levels. A trained assessor also performed a comprehensive walk-through of each participant's home and quantified visible mold and water damage. The children were examined for the presence of allergic disease annually at ages 1-4 and again at age 7 where asthma was objectively diagnosed via pulmonary function testing and methacholine challenge. Parents filled out a detailed questionnaire at each exam. DNA and hair samples were collected at each research visit and nicotine and cotinine has been quantified in the hair samples from ages 2, 4 and 7. All children's DNA samples have been genotyped on a custom SNP array, which included genes related to asthma, eczema, oxidative stress and nicotine metabolism. Serum samples were collected on ~25% of the cohort at age 7.

3. Ohio Pediatric Asthma Repository (OPAR)

The central objective of the Ohio Pediatric Asthma Repository (OPAR) is to build a comprehensive biorepository linking clinical, demographic, adherence, health literacy, environmental, and health outcomes data, which could be used to better understand asthma phenotypes and to determine the practices across the participating OH children's hospitals that were associated with the most optimal outcomes. A secondary objective was to provide a resource to stimulate collaborative research in

asthma. The six participating Ohio Children's Hospitals are Cincinnati Children's Hospital Medical Center, Nationwide Children's Hospital, Dayton Children's Hospital, Akron Children's Hospital, Rainbow Babies and Children's Hospital, and ProMedica Toledo Children's Hospital. Participants between the ages of 2-17 admitted to the hospital with a diagnosis of asthma, wheezing, or reactive airway disease (RAD) were eligible to participate. The participant's parent or legal representative is asked to complete questionnaires used to collect demographic information, medical history, environmental exposures, and adherence to medications for the participant and his/her family, if applicable. Information from the participant's hospital stay, including initials, date of birth, consent status, questionnaire completion status, incentive money status hip and waist measurements, times of admission/discharge to the ED/Floor/ICU, measurement tools used, drugs administered, healthcare provider, discharge medications, discharge diagnoses and education provided. Nearly 3500 participants have been enrolled thus far and biospecimen collection is now being added to the process.

OBESITY:

Obesity (BMI above 95th percentile) affects about 17% (12,924,186) of children in this country. Severe obesity (Class 2 and 3, or 20% or more above the 95th percentile [corresponding to BMI of ≥ 35 at age 18]) affects about 6%, or 4,374,672 children.

Therefore, severe obesity in children is as common as asthma, another chronic health condition of childhood. Like obesity, asthma is also linked to environmental triggers. Severe obesity is more common than childhood cancer, congenital heart disease, celiac disease, cystic fibrosis, and autism combined.

Most of these severely obese children will need to manage obesity (and the common comorbid illnesses like hypertension, type 2 diabetes, and sleep apnea) as a chronic condition for the rest of their lives, with few proven long-term treatments. The costs for healthcare over the lifetime for this generation will be enormous. We must act now to better understand this extreme phenotype and discover how to reverse it.

Our bariatric surgery team has banked DNA and serum specimens on 177 teenagers with severe obesity here at CCHMC. We have also saved specimens from another 100 similar teens from other sites within the Teen LABS consortium and are happy to work with others to use these extant cohorts for future discovery.

Our Endocrinology clinic for infants and children up to 5 years of age with severe obesity or unexplained, rapid weight gain is now in its fifth year and receives 30-40 new patient referrals a year. Each child is evaluated for genetic and endocrine causes of early onset/severe obesity.

DIABETES MELLITUS:

The Diabetes Center in Endocrinology has 2,260 active patients: 1,876 individuals with type 1, 136 type 2, and 248 other types. The diabetes team sees over 230 newly diagnosed patients each year. These individuals participate in ongoing research protocols focused on the epidemiology of diabetes; the natural history of diabetic complications (cardiovascular, peripheral vascular, renal, CNS); the role of lipids in vascular complications; self-management of diabetes; and defining the cause of beta cell dysfunction in non-autoimmune diabetes.

Since 2006, NICHD has supported three interrelated prospective cohort studies of fertility, miscarriage, and birth outcomes in Denmark and North America.¹⁻²³ Smart Gravid (SG) enrolled over 5,000 Danish women.^{1,2} Smart Forældre (SF), a successor to SG, was launched in 2011 and has enrolled over 3,300 women and 360 men. Pregnancy Study Online (PRESTO) has recruited 2,556 women and 728

men from the U.S. and Canada.²² SF and PRESTO are still ongoing. After completing online eligibility and baseline surveys, women are followed bi-monthly for up to 1 year. Women who conceive complete surveys at 8-11 and 32-35 weeks' gestation. Men complete a baseline survey. Detailed data are collected on lifestyle, behaviors, diet, medical and reproductive history, and stress. Resources in Denmark enable linkage with registry data on birth outcomes, child obesity, and inpatient and outpatient visits.^{12,20,23} PRESTO links with selected U.S. birth registries. Biospecimens (urine and blood) have been collected in a subset of women (106 in SF; 75 in PRESTO) and several environmental chemicals have been measured; PRESTO has enrolled a diverse cohort (25% minority).

Our studies represent a unique birth cohort resource. The web-based infrastructure is already established and can be easily modified to incorporate new hypotheses. Additional strengths include the prospective design, high cost-efficiency (\$140-\$160/participant), registry linkage, detailed covariate data, and preconception enrollment thereby allowing examination of multiple critical windows of susceptibility. Birth registry data include birth and placental weight, gestational age, head circumference, and maternal medical conditions. The studies could be expanded to collect placental tissue, cord blood, and further health outcomes among children. Added exposure data could be incorporated via use of silicone wristbands as passive samplers,²⁴ air pollution monitors, and biomarkers in saliva, hair, and toenails. The inclusion of male partners creates opportunities for more comprehensive analyses of paternal and maternal influences on child health.

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