COMPILED RESPONSES[1] TO REQUEST FOR INFORMATION ON ENHANCING THE SCIENCE OF THE ENVIRONMENTAL INFLUENCES ON CHILD HEALTH OUTCOMES (ECHO) PROGRAM – NOT-OD-21-129

Respondent 1

To Whom It May Concern,

Thank you for the opportunity to provide input on enhancing ECHO science. As a scientist who is an ISPCTN site PI and a Protocol Chair, I am definitely an "insider" in this program. My overwhelming view of the ECHO program is that it is extremely valuable and meeting many of the targets of the program to enhance the health of children for generations to come. In my view, both the cohort side and the ISPCTN side of ECHO are gaining momentum in accomplishment many key tasks along this road of discovery and productivity. Therefore, the comments I offer below should be considered in this context.

First, I would suggest that the ISPCTN needs processes that allow it to be more nimble and responsive to trials and trial ideas. Scientific rigor and network cohesion are important, but at this point these and other factors are slowing the network from proceeding as nimbly as we need to.

Second, I would submit that we need greater cohesion/cross-talk between the ISPCTN side and the cohort side of ECHO. The Discovery talks are a great way to increase this collaboration, but more formal and routine cross-talk will allow for greater focus across the network in identifying solution- oriented scientific questions. For example, one of the general topics listed in this solicitation is about recruitment, but the ISPCTN just completed a study where different recruitment methods were assessed in a randomized fashion. I am not sure if these results are being shared on the cohort side? Processes to do so on a larger scale may be helpful to this type of cross-talk and solution-oriented focus.

Again, I offer these comments in view of my overwhelmingly favorable view of ECHO and my gratitude for being able to work with this team.

Respondent 2

Hello,

We would like to submit comments/suggestions related to topics NIH outlined in the request.

1. Approaches to promote scientific value while reducing burden on participants and staff in large consortia of parent-child cohort studies that involve primary data collection, including but not limited to

[1] All responses appear as received – the only edits were to remove attribution.

Innovative tools and approaches for remote data and biospecimen collection in large epidemiologic studies

Use of non-invasive devices for collecting e.g., environmental data, behavioral data, and physiologic-- such as monitors for the home to collect air quality data, or wearable sensors and other devices that get activity, location, heart rate, breathing rate, skin conductance, etc.

2. Engagement strategies to enhance recruitment and retention of diverse study populations

Creating and sending newsletters to study population to enhance engagement; providing study updates and outcomes periodically/annually; participation options in studies and supplemental studies

3. Preconceptional Origins of Child Health Outcomes:

Physical and chemical exposures

Inclusion and collection of parent/maternal newborn blood spots

Respondent 3

Dear ECHOProgram:

My comments and perspective follow:

I. General Topics

Approaches to promote scientific value while reducing burden on participants and staff in large consortia of parent-child cohort studies that involve primary data collection, including but not limited to

Innovative tools and approaches for remote data and biospecimen collection in large epidemiologic studies: The placenta is the interface between mother and baby. While other organs of the human (and other animal) bodies are generally a similar configuration with size relative to the human/animal who requires its function, the placenta is effectively an amoeba, with variations in cord insertion and shape of the placental disk, which is the sole source of oxygen and nutrients for the fetus throughout gestation. We and others have shown that these variations can be (albeit crudely) timed, that they can be accounted for by perturbations in vascular arborization, and that they are associated with reduced placental efficiency which may mark, mediate or moderate effects of the environment that cause these shape changes on the fetus. Finally, placental histopathology types have been linked to sex-specific changes in levels of developmentally important regulatory molecules in the newborn circulation. The more "complex" the placental structure, the poorer the ability to capture the variations with simple ruler measures, and the greater the need to capture them if we want to understand the fetal environment as it relates to lifelong health risks. 3D scan, chorionic surface photographs to document the surface vascular pattern, and carefully oriented tissue sections are important to collect. The 3D scan and surface photos preserve gross features that are appreciated to be unique to each child so that such features can be preserved in their full complexity, and analyzed by current and yet-to-be-developed technology and correlated with future health measures. The tissue slides can be digitized so that they too can be preserved to present and future analyses.

Balance of essential and recommended protocol elements These measures can be performed on site or shipped to a central site at room temperature within a week or two of delivery, which makes them amenable to collection at any hospital in the US or the developed world.

II. Preconceptional Origins of Child Health Outcomes:

Identifying solution-oriented ("so what") scientific questions about preconceptional origins of child health outcomes, based on knowledge from pre-clinical, clinical work, and population research, including but not necessarily limited to the following preconception factors:

Obesity and lifestyle factors such as diet, sleep, physical activity: Do placental size/shape, gross and microscopic vasculature and histopathology types mark, mediate or moderate influences of maternal diet, disease and environmental exposures on newborn and childhood metabolic set-points and physiology.

Physical and chemical exposures: Do placental size/shape, gross and microscopic vasculature and histopathology types mark, mediate or moderate effects of physical and chemical antenatal exposures, and life long response to such exposure?

Fathers: Are placental size/shape, gross and microscopic vasculature and histopathology types dependent upon paternal factors such as epigenetic modifications that increase with increasing paternal age?

Psychosocial and societal influences: Do placental size/shape, gross and microscopic vasculature and histopathology types mark, mediate or moderate effects of prenatal stress?

Measures and biospecimens from prospective mothers and fathers that cohorts should collect prior to or in early pregnancy, including among the 3 sources of potential participants above: The placenta is the single biospecimen that carries the scars or enhancements of environmental exposures across gestation.

Thank you for your consideration.

Respondent 4

Please see below some thoughts about some components of this RFI, in red. Best,

Optimal frequencies of data collection: Annually for questionnaire-based or remote-based data collection; At least once in most lifestages for most biospecimens (e.g., metabolic markers like glucose, lipids, etc, don't change that much at this age- one exception may be puberty).

Balance of essential and recommended protocol elements: Essential or core elements should be minimal (e.g., socio-demographic data, residence, core measure for main outcomes); Most other elements should be recommended, with clear recommendations for data collection tools and approaches, and harmonized.

Nimbleness to address public health emergencies in large collaborative consortia of longitudinal studies: Very important, as we have seen with the COVID19 pandemic. The more policies and procedures, committees, subcommittees, groups and subgroups we put in place, each with their own structures, goals, metrics, etc, the less agile we become and the harder it is to address public health emergencies, because we would have spent all our energy on process. As hard as it may be, we have to let go of some rigid structures (e.g., semi-annual goals and metrics of success for

working groups; annual GOITs, meetings to plan meetings, etc). Simpler and more agile structures, ad hoc working groups, seamless additions or removal of protocol elements, smaller number of committees. Just keep the essential ones (e.g., Steering, Publications, Protocol Oversight). I don't think we need "science-oriented" committee and working groups but rather more agile structures that permit investigators to get together and think about projects. When possible, in person meetings, organized around specific scientific issues/areas of interest – more like workshops.

Engagement strategies to enhance recruitment and retention of diverse study populations: Diverse study staff that can relate better to diverse participants; Retention events that are fun and engaging for participants and staff; Less pressure on staff with target numbers and data -related deadlines. Stressed staff won't be engaged, efficient and dedicated and that will hurt recruitment (especially of diverse participants) and data quality.

Promotion of diversity of the scientific workforce related to child health. I'd like to see that reflected more in the leadership of studies like ECHO, not only in the scientific workforce. With respect to the scientific workforce, I conceptualize diversity rather broadly.

II. Preconceptional Origins of Child Health Outcomes:

Identifying solution-oriented ("so what") scientific questions about preconceptional origins of child health outcomes, based on knowledge from pre-clinical, clinical work, and population research, including but not necessarily limited to the following preconception factors:

Obesity and lifestyle factors such as diet, sleep, physical activity. Better understanding of why obesity and lifestyle factors during pregnancy are so strongly elated to childhood obesity and metabolic health, yet the vast majority of lifestyle pregnancy interventions are not successful. To me, this is an important question to address before launching (potentially more) expensive lifestyle preconceptual interventions. An initial approach would be to study various lifecourse models exploring the role of such exposures during specific "sensitive" periods (pre-conceptual, pregnancy, infancy, etc) in terms of their impact on child obesity, and then understand the pathways through which they may operate (biologic, social, societal).

Fathers: Epigenetic contributions to transgenerational effects (fathers and mothers). Psychosocial and societal influences: Understand how social and societal factors interact with biology, genetic predisposition and epigenetic factors in shaping specific outcomes.

Strategies for recruiting participants preconceptionally, and retaining through pregnancy into childhood

Feasibility of different strategies, including ensuring adequate sample sizes of births and participant diversity, from Young women and men, already participating in ECHO cohort studies, entering reproductive age: Quite feasible, should be a high priority; Women with a recent pregnancy in ECHO, and their partners, who may have a subsequent pregnancy; Feasible, though would discard the data already collected by ECHO on current pregnancies/offspring (unless they are also followed up until their enter the reproductive age). Women and men of reproductive age irrespective of previous participation in ECHO: Has nothing to do with ECHO; should be a different study. Definitely possible though- see data and publications from the defunct National Children's Study.

Measures and biospecimens from prospective mothers and fathers that cohorts should collect prior to or in early pregnancy, including among the 3 sources of potential participants above: We

certainly have ideas that we would discuss in a grant application. Also, see data from the National Children's Study

Respondent 5

We are a consortium of preconception cohort studies, incorporating data from over 20 studies. Our consortium (Preconception Period Analysis of Risks and Exposures Influencing Health and Development; PrePARED), was developed in an effort to address important scientific questions about the preconception period in relation to reproductive, perinatal, and pediatric (RPP) health outcomes. Consortium investigators recognize that the preconception period is understudied relative to the pregnancy and postpartum periods, despite its critical importance for long-term health outcomes for mothers and children. The preconception period is an important opportunity for health and behavior change interventions that can positively shape the health of women, their offspring, and their families. According to the U.S. Centers for Disease Control and Prevention, "Eliminating disparities in preconception health can potentially reduce disparities in two of the leading causes of death [for women] in early and middle adulthood (i.e., heart disease and diabetes)." Preconception is also a key time for addressing pregnancy health disparities: in the U.S., Black and Hispanic women are at higher risk for adverse preconception exposures, including poor nutrition, cigarette smoking, racial discrimination, depression/anxiety/stress, environmental chemicals, chronic diseases, and limited access to care. In the course of developing our consortium, we have considered many of the questions raised by the RFI.

I. General Topics

- Approaches to promote scientific value while reducing burden on participants and staff in large consortia of parent-child cohort studies that involve primary data collection, including
    - Balance of essential and recommended protocol elements

We have addressed this by requiring a minimal set of data from studies for consortium participation which would be necessary to address almost any RPP outcome, and determining which studies will participate in analyses based on additional data available.

- Nimbleness to address public health emergencies in large collaborative consortia of longitudinal studies

Two major needs under such circumstances are rapid funding and human subjects approval. These could be addressed by having a procedure by which prespecified protocols are approved in general terms by each IRB, which could be quickly re-reviewed and approved to address a specific event. Small amounts of funding to assist with this process, to be followed by more extensive rapid grants when emergencies arise, would be one approach to facilitate nimble science in such consortia.

- Engagement strategies to enhance recruitment and retention of diverse study populations

This may be improved by incorporating studies that have proven records of recruitment and retention directed specifically at diverse populations of interest interest and with demonstrated commitment to community engagement; by combining data from multiple studies in multiple geographic area, there is diversity in the pooled studies even if the individual studies are limited

to single populations. In addition, we suggest the incorporation of international cohorts, as many of these issues do not stop at the national border.

- Promotion of diversity of the scientific workforce related to child health

A diverse workforce could be supported by encouragement of new proposals with diverse and inclusive study teams, as well as offering diversity supplements, both of which are likely to improve recruitment and retention of diverse populations as well.

II. Preconceptional Origins of Child Health Outcomes:

- Identifying solution-oriented ("so what") scientific questions about preconceptional origins of child health outcomes, based on knowledge from pre-clinical, clinical work, and population research, including but not necessarily limited to the following preconception factors:

Overall, important goals should be identifying critical periods and timelines for interventions, including the time periods where women may be more motivated to change health behaviors and setting that may be most effective to promote health behavior change; identifying independent effects of preconception exposures (as opposed to those which may merely correlate with exposure levels during pregnancy); assessing effects among both planned and unplanned pregnancies; and addressing heterogeneity and interaction by covariates such as race/ethnicity, maternal age, and location. Investigating associations between the various exposures and key reproductive outcomes (such as time to pregnancy and miscarriage), in addition to perinatal outcomes, and the health of the child and of the biological parents is critical to a full understanding potential causal relationships. Few preconception interventions have been rigorously evaluated.

Obesity and lifestyle factors such as diet, sleep, physical activity: Important scientific topics include: the extent to which effects of obesity on pregnancy can be effectively mitigated by health behaviors during the preconception period; the degree to which intentional weight loss attempts improve or worsen outcomes, considering effects among those who are unsuccessful or rebound during pregnancy or later; optimal yet achievable recommendations for diet and physical activity; and when clinical or public health recommendations should be put into place, balancing concern about pregnancy and next-generation health with respect for autonomy and varied reproductive intentions, including recommendations to delay pregnancy in order to institute behavioral changes.

Physical and chemical exposures: Important scientific questions include: the extent to which preconception exposures have effects independent of or additive to exposures during pregnancy or levels measured during pregnancy, and whether diet and nutrition can mitigate effects of chemical exposures.

Fathers: Important scientific questions include: The extent to which there are independent, biological effects of paternal preconception exposures, and if so, biological mechanisms for their effects. Paternal exposures are particularly important if epigenetic mechanisms are being considered, as animal studies often indicate effects via the paternal line. Including studies with information on fathers, as several of our cohorts have, allows for ability to control for confounding by male partner characteristics. From a translational perspective, an important

question is whether preconception interventions can be more effective when they target the family unit/couple, rather focusing strictly on the mother.

Psychosocial and societal influences: Important scientific questions include: comprehensive assessment of the effects of adverse childhood experiences, stress and traumatic experiences, mood disorders (particularly maternal depression) on RPP health outcomes; long-term and transgenerational effects of racism and discrimination; whether these factors have direct biological effects (e.g., via stress hormones), or have effects primarily mediated through differential access to societal resources (e.g., access to healthy foods, health care, education, occupation, income, wealth), correlated behaviors (smoking) or postpartum mental health; how all these factors contribute to health disparities.

- Strategies for recruiting participants preconceptionally, and retaining through pregnancy into childhood
    - Feasibility of different strategies, including ensuring adequate sample sizes of births and participant diversity, from
        - Young women and men, already participating in ECHO cohort studies, entering reproductive age
        - Women with a recent pregnancy in ECHO, and their partners, who may have a subsequent pregnancy
        - Women and men of reproductive age irrespective of previous participation in ECHO

Broadly considered, preconception studies have three options: 1) recruit pregnant women and retrospectively collect data on the preconception time frame, either from records or interview; 2) recruit couples actively attempting pregnancy; 3) follow reproductive-aged individuals and assess pregnancies when they occur.

Advantages to Young women and men, already participating in ECHO cohort studies, entering reproductive age: efficient, captures both planned and unplanned pregnancies.

Disadvantages to #1: does not include sterile couples, may produce recall bias or bias in biomarkers whose levels are affected by time or pregnancy itself

Advantages to Women with a recent pregnancy in ECHO, and their partners, who may have a subsequent pregnancy: efficient, allows for detailed examination of the period prior to pregnancy, includes couples along the full spectrum of fertility (including those who conceive quickly, who never conceive, and who take longer than 12 months), allows full ascertainment of pregnancy outcomes other than live birth, allows for longitudinal data collection on changes in risk factors, particularly behavior

Disadvantages to Women with a recent pregnancy in ECHO, and their partners, who may have a subsequent pregnancy: couples planning pregnancy are not representative of all pregnancies and offspring; they may have better health behaviors but may also be more likely to be subfertile, especially if they are older or wait to enroll in the study, even for a month or two after trying to conceive

Advantages to Women and men of reproductive age irrespective of previous participation in ECHO: more generally representative, captures both planned and unplanned pregnancies, includes individuals who do not conceive (either intentionally or unintentionally), Able to collect

all pregnancy outcomes. Collects preconception information during the preconception period, including on natural history of behavior and behavioral changes, and does not suffer the limitations of retrospective assessments.

Disadvantages to #3: requires greater investment of time and sample size to capture the same number of pregnancies, and timing of study visits relative to pregnancy may not be consistent (unless visits are very frequent).

A special case of Women and men of reproductive age irrespective of previous participation in ECHO is to recruit women during pregnancy and follow them for subsequent pregnancies; this approach offers many of the advantages of #3, while it enriches the sample for fertile couples and those who want more children. It also allows for assessing the impact of interpregnancy health behavior changes.

Another special case of Women and men of reproductive age irrespective of previous participation in ECHO is to follow young people as they enter reproductive years. For example, if young people enrolled in ECHO as children are followed for pregnancy, this allows for examining possible multigenerational effects.

- Measures and biospecimens from prospective mothers and fathers that cohorts should collect prior to or in early pregnancy, including among the 3 sources of potential participants above

At a minimum, information for cohorts participating in our consortium is available on maternal age, race, education, parity and gravidity, tobacco use, BMI, and outcome of any pregnancies (livebirth, miscarriage, stillbirth). In addition, it is necessary to know calendar year of any measurements and the time between the measure and the pregnancy.

Most studies in our consortium also include information on pregnancy complications such as hypertensive disorders, birth outcomes, pre-existing chronic conditions such as hypertension and diabetes, weight gain during pregnancy, alcohol and other substance use, and income. Additional key information includes time to pregnancy (which can be assessed retrospectively, but must be detailed), and the use of any fertility treatments to conceive, particularly any use of donor gametes. Paternal demographic information is highly desirable.

Blood and urine are the most generally useful biospecimens.

Respondent 6

To Whom it May Concern,

Thank you for the opportunity to offer feedback for the ECHO program. I have been studying Black American youth's racial discrimination experiences for over 20 years and earned a Ph.D. in Developmental Psychology. I have expertise in understanding the prevalence of racial discrimination experiences, the impact of those experiences on Black youth's mental health and overall development, constructs that interrupt the effects of racism on Black youth's development and mental health, and specific contexts where racial discrimination is most likely to occur. I am currently an associate professor in the School of Family and Social Dynamics at Arizona State University. I spend most of my professional time conducting research on Black youth's experiences with racism and I have over 50 peer-reviewed publications on this topic. The

Society for Research on Adolescence commissioned me as the lead author to write a consensus statement detailing the impact of racism on Black youth. Last summer, I organized and co-hosted an antiracism webinar for the Society for Research in Child Development on June 30, 2020. Last summer, I also participated in a Town Hall discussion on racism organized by my local PBS station. I am recognized as an international expert on racism, especially as it pertains to understanding the impact of racism on Black youth's development and health.

Promotion of diversity of the scientific workforce related to child health

I have perused the ECHO-wide Cohort Data Collection Protocol, and noticed something striking. The leadership team includes all White individuals despite the fact that the majority of youth under the age of 15 are non-White (Frey, 2019). Where are the Black, Latinx and Asian and members of the ECHO leadership team? Two of the largest organizations dedicated to the study of child and adolescent development include the Society for Research in Child Development (SRCD) and the Society for Research on Adolescence (SRA). I have been a long- standing member of both organizations and they include significant numbers of Black, Latinx, Asian and Native American scholars with expertise in their respective populations. SRCD includes the Black, Asian, and Latinx caucuses, and the Ethnic and Racial Issues Committee and the Equity and Justice Committee. Yet, the leadership team for the ECHO program is all White. Why was it acceptable to organize a large scientific study of children in the United States without a diverse leadership team? This needs to be rectified immediately! The noticeable lack of diversity in the leadership team is related to the second point that I wish to make.

Psychosocial and societal influences

While perusing the ECHO-wide Cohort Data Collection Protocol, there are no measures of racism for the parents/guardians or the children despite the fact that racism is a significant environmental factor for child and adolescent development. For example, racism is felt in utero among Black American youth. Previous research has shown that maternal racial discrimination experiences were linked to adverse birth outcomes such as low birthweight, preterm birth, and small for gestational age among ethnic-racial minority women (Alhusen et al., 2016). Racial discrimination is experienced by Black youth when they enter preschool between the ages of three and four. The US Department of Education released data showing that although Black American children represented 18% of preschool enrollment, they comprised 42% of preschool students suspended once and 48% of preschool students suspended more than once (US Department of Education, Office for Civil Rights, 2014). Black

American youth experience racial discrimination early in life and prior to formally starting school. Black American youth demonstrate knowledge of negative racial stereotypes about their racial group around age six (Pauker et al., 2010), and experience racial discrimination early in middle childhood (Coker et al., 2009).

The protocol includes the Everyday Discrimination and Experiences of Discrimination, which assess general discrimination. General discrimination is not equivalent to racial discrimination (e.g., the behavioral component of racism) or racism-related experiences. I want to reiterate that the current ECHO protocol does not include assessment of child/adolescent or parent/guardian experiences of racism or racial discrimination, which is a huge problem. Given that racial discrimination experiences increase during childhood and adolescence (Greene et al., 2006), there should be annual assessments of racial discrimination for the ethnic-racial minority parents/guardians and children.

Furthermore, the physical environment measures don't include assessments of institutional racism, which does the most harm to ethnic-racial minority children and adolescents (see Seaton, 2020). Where are assessments related to whether families reside in a food desert, near a toxic waste site, and/or near a hospital? Where are assessments related to police indicators since ethnic-racial minority neighborhoods tend to be overpoliced, which is a risk factor for being swept into the penal system? All of these are indicators of institutional racism that are lacking in the current ECHO protocol. This needs to be rectified immediately.

I truly hope that the ECHO leadership team responds to this feedback and incorporates non-White scholars into the leadership team, and racism related measures into the protocol. I am happy to talk further if desired.

References

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Learn more about racism!

Respondent 7

Dear NIH ECHO Program Office,

In response to the Request for information (RFI) on enhancing the science for the Environmental influences on Child Health Outcomes (ECHO) program, Notice Number: NOT-OD-21-108, please see comments below addressing some topics mentioned in the notice.

Has sibling recruitment been considered?

There is a need to address approaches to reduce burden on participants and staff. Suggestions for doing so include: 1) lessen the administrative work on PIs; and 2) allow cohorts to carryover funds in a more seamless and less cumbersome manner to facilitate study staff retention, maintenance of cohort recruitment and retention, collection of high quality data, and dissemination of key research within and across ECHO sites. The yearly closeout process creates a huge administrative burden on PIs and staff that directly takes away from field collection and analysis efforts and money for research is typically inaccessible for 1-2 months or more each year due to university administrative bureaucracy beyond the PI's control.

While it is important to consider preconception stage (recruitment/retention), adding more elements of data collection to the current ECHO-wide Protocol would likely continue to increase burden on cohorts.

An inherent problem with preconception is that you target the organized couples with distinct plans to have children and you do not capture unintended pregnancies thus causing bias. The same can be said for using participants from fertility clinics. How is this potential for bias being addressed or considered?

Respondent 8

Here are my comments from the live stream event:

Are there any existing population based studies that look at factors related to a successful vs non-successful pregnancy?

Pregnancy leading to a live birth

The reason I asked this is because there was discussion about the path forward for the now adults in the childhood cohorts of which my cohort is one. And with the size and scope of echo it might be interesting to look at not just the environmental influences of pregnancy complications but also the social choices of pregnancy with a new generation of adults. Are there factors that lead to an increased or decreased birth rate among certain populations. Are those factors related to prior childhood health complications, environmental influences, etc?

With the size of echo and the current state of marijuna laws across the country it might be interesting to look at factors related to state drug laws and how those laws affect childhood or family health in either a positive or negative way if that's not already being considered.

I think my comment here is pretty self-explanatory. The US currently has very different marijuana laws regionally. There may not be a better time to look at the implications of relaxed marijuana laws in an exposed population vs a reference population. Does the law impact the level of marijuana use in the home, the amount that children are exposed to, does this lead to an increased number of medical complications, airways issues, are there benefits? The challenge would be in getting honest reporting of illegal activity in the reference populations with not-relaxed marijuana laws. You may even be able to look at this temporally within regions that recently changed or will change in the near future.

Generally I think the greatest value to echo is in its size and diversity, analyses that may otherwise not have statistical power when stratified in smaller populations is a great and valuable

use of echo but are there analyses that echo can do that smaller more isolated populations just can't accomplish on their own? Are there regional effects to healthcare, are there fundamental differences in the populations, are their societal or economic differences that persist or don't persist regionally?

Respondent 9

Hello,

I attended the presentation last Thursday on the environmental influences on child health. My close friend Dr. Leslie Thompson, who works in your department, speaks very passionately about the work that he does.

Despite me not having any related experience or knowledge to this field of study, I feel like the team did an excellent job presenting what they're seeking to do. I may not have understood all the technical terms but what I did get out of it is that the team is doing very important work to better understand the different factors that may affect child health.

I appreciate how you made this open to the public and kudos to Dr. Thompson for making it known that I could attend!

As a lay person, I would be interested to learn more about what your department discovers regarding the various contributors to the health of children. I think it will provide valuable information so the public can have a better understanding on how to raise children and see to it they live healthier lives.

Thank you for the time you took for the presentation!

Respondent 10

Included below are some "cutting-edge" papers that should be of interest to the organizers of this meeting. It fits directly into the underlying mechanism that is the theme of the ECHO Preconception Workshop.

If there are any questions, please do not hesitate to contact me.

1) Trosko JE (2018) Modulation of Cell-Cell Communication and Epigenetic Mechanisms as a Shared Cellular Mechanism in Diverse Childhood Brain Diseases, Such as Cancer and Autism. *EC Neurology* 10.3: 134-156.
2) Trosko JE (2016) A Conceptual Integration of Extra-, Intra- and Gap Junctional Intercellular Communication in the Evolution of Multi-cellularity and Stem Cells: How Disrupted Cell-Cell Communication during Development can Affect Diseases later in Life. *Int J Stem Cell Res Ther* 3:021
3) Trosko JE (2011) Pre-Natal Epigenetic Influences on Acute and Chronic Diseases Later in Life, such as Cancer: Global Health Crises Resulting from a Collision of Biological and Cultural Evolution. J Food Sci Nutr 16:394-407. DOI: 10.3746/jfn.2011.16.4.394

Respondent 11

Response to "Request for information (RFI) on enhancing the science for the Environmental influences on Child Health Outcomes (ECHO) program"

Notice Number: NOT-OD-21-108

One of the biggest challenges in longitudinal research is identifying engagement strategies to enhance recruitment and retention of diverse study populations. This is an area where the NICHD-funded Fragile Families and Child Wellbeing Study (FFCWS) has been particularly successful, and perhaps our experience and approach can be informative for ECHO.

FFCWS has followed a large and diverse sample of families with newborns since 1998, with interviews at birth and at age 1, 3, 5, 9, 15, and 22. We are now in the field interviewing the children at age 22. We are also interviewing the person who was the primary caregiver (PCG) when the child was 15 (typically the mother).

We have been extremely successful at retaining a high proportion of our diverse sample. At our most recent completed wave, age 15, 77% of eligible PCGs and 74% of eligible teens participated.

Our survey firm Westat has used birthday cards, address updates, P.O forwarding, phone communication, and web-based interim tracking to maintain contact with participants between waves of data collection. The web-based interim tracking system allows respondents to enter and update their own contact information and provide information for an additional contact person. Participants have also provided social media account information, which can also be used to help locate hard-to-reach respondents.

Once the survey is underway, we make numerous attempts to contact participants. For our age 22 wave, on the initial launch week (week 1) for each case, all participants with viable addresses are sent a postal-mail letter, and an email if the study has an email address. If permission to text has been obtained, two text messages are sent to announce the survey.

Until the primary caregiver begins the survey, they receive:

- If viable mailing address: A reminder postal-mail letter on week 5.
- If email: reminder emails on weeks 2, 4, 6, and 8
- If text permission: reminder texts on weeks 2, 3, 5, 7, and twice on week 8

Until the Young Adult begins the survey, they receive:

- If viable mailing address: A reminder postal-mail letter on week 5.
- If email: reminder emails on weeks 2, 4, 6, and 8
- If text permission: reminders twice a week for weeks 2 through 8. We have modeled this schedule after other surveys of young adults.

Regarding interviewer contacts, our field approach is not a call-center type of design. Each case has a deep history to be reviewed and taken into consideration, and one interviewer is assigned the PCG and YA cases for a family and asked to develop a personalized approach to each case.

Finally, we expect the web-based survey option which we are implementing at the age 22 wave will increase response rates by providing young adults with greater choice and flexibility to

participate at their preferred time and pace. Already we are seeing faster response rates due to the web-based option.

We hope these comments will be helpful.

Respondent 12

Dear Dr. Artega:

As Deputy Director of the ongoing Canadian CHILD Cohort Study (N=3500 families with children born in 2010- 12; www.childstudy.ca), I am familiar with the challenges and opportunities in birth cohort research. As director of the $5M International Milk Composition (IMiC) Consortium (www.milcresearch.com/imic N=1200 dyads, 4 countries) and co-Director of the Manitoba Interdisciplinary Lactation Centre (www.milcresearch.com), my research is dedicated to understanding the determinants and consequences of variation in human milk and infant feeding practices in longitudinal parent-child cohort studies. Over the past year, I have been an active member of the NIH Breastmilk Ecology: Genesis of Infant Nutrition (BEGIN) initiative focused on defining research priorities in this field.

At MILC, we host a human milk biorepository and specialize in comprehensively analyzing the diverse nutritive and non-nutritive components of human milk. We work with the top milk science labs in the world, and collaborate with machine learning experts to integrate these multi-omic milk datasets using 'understandable artificial intelligence' approaches to investigate human milk as a biological system (many components) within a system (the mother-infant dyad). We have experience sending, receiving and tracking human milk samples internationally, optimizing analytical protocols for milk, and minimizing required sample volumes.

I believe ECHO has a unique opportunity to contribute new knowledge in the field of infant feeding and human milk composition. With this in mind, I will comment on two specific RFI Topics.

Topic 1: "Approaches to promote scientific value while reducing burden on participants and staff in large consortia of parent-child cohort studies that involve primary data collection, including Innovative tools and approaches for remote data and biospecimen collection in large epidemiologic studies."

Mother's milk is recommended as the sole source of nutrition for the first 6 months - a critical period of early postnatal development. Breastfeeding is arguably the most important "Environmental Influence" on the newborn microbiome, which affects all aspects of infant development. I strongly encourage your team to ensure that infant feeding practices and human milk composition are addressed in the ECHO Program.

Infant feeding data can be self-reported by online survey. This is a critically important but complicated 'early life exposure' to capture in birth cohort studies. Many studies have done a very poor job of capturing infant feeding patterns - for example, many fail to capture breastfeeding duration and/or exclusivity, and almost none have captured pumped milk, which is fed to over 85% of US infants today. Pumped milk is not equivalent to milk fed directly from the breast, so this distinction is very important.

Breast milk can be collected at home by hand or pump expression, frozen in a home freezer and returned by mail. Depending on the assays planned, it can also be collected on filter paper, dried,

and returned by mail - much like a dried blood spot. I have recently co-authored a book chapter about human milk collection for research. At the MILC biorepository, we specialize in collecting, storing and comprehensively analyzing the diverse nutritive and non-nutritive components of human milk.

I would be happy to provide additional information and/or consult with ECHO investigators about collecting feeding data and milk samples, including the optimal frequency and the balance of essential vs recommended protocol elements.

Topic 2: "Nimbleness to address public health emergencies in large collaborative consortia of longitudinal studies."

During the COVID-19 pandemic, I launched two large new collaborative studies: the CHILD Cohort Study COVID- 19 Add-On Study (N>5000 individuals from 1500 families in 4 provinces,) and the International Perinatal Outcomes in the Pandemic (iPOP) Study (www.ipopstudy.com, >150 collaborators in 41 countries).

Both studies are addressing key questions from policymakers related to the pandemic, and involve regular engagement of these and other stakeholders to ensure that we are asking and prioritizing meaningful questions and rapidly translating results back to these individuals in order to inform decisions. While iPOP is a brand new platform, CHILD has existed for more than a decade. We have been able to 'nimbly' pivot and expand the CHILD platform to address the urgent and evolving needs of policymakers in the current public health emergency. I have learned many lessons during this process - from what to ask and who to engage, to obtaining streamlined approvals and implementing new protocols for remote research. I would be happy to share my experience with the NIH ECHO team.

I hope this information is helpful, and look forward to connecting with the ECHO team to explore opportunities for consultation or collaboration.

Respondent 13

Dear ECHO planning group

Unfortunately, I am unable to attend today's webinar, but I would like all involved in this effort to recognize and acknowledge the two biases that occur repeatedly in preconceptional research and that limit the generalizability of findings unless cohorts are assembled preconceptionally in ways that avoid these biases. I write to you because the address provided in the email for comments seems not to be functional (NIHKidsandEnvironment@od.nih.gov.)

Both biases emerge from the pre-conceptional pool usually used to assemble preconceptional cohorts, that is to say, women planning a pregnancy.

The first bias is fairly straightforward. Surveys have repeatedly shown that only about half of pregnancies in the US are planned, and the characteristics of pregnancy planners and non-planners are likely to be very different.

The second bias is a function of the ordinary way we approach women planning a pregnancy, which is, in effect, a prevalence survey, and thus dependent on duration of the state we ascertain which is the preconceptional interval. The interval between deciding to get pregnant and actually getting pregnant is quite short in most non-contracepting women. Studies have shown that about

25% of women get pregnant in the first cycle, and another 25% in the second cycle. The chances of identifying such women on any form of cross- sectional survey is very small. Thus the women we succeed in talking to and enrolling in studies pre-conceptionally are planners with longer pre-conceptional intervals.

Virtually all studies involving preconceptional cohorts as usually assembled thus tend to be composed nearly entirely of women who plan pregnancies and who do not get pregnant in the first few cycles. These factors are likely associated with age, with socio-economic status, with fertility and with much else. Whether this matters to the research undertaken in such women depends on the study's hypotheses, but it is important to be aware of the limitations to generalizability emerging from such studies.

Is it possible to assemble a preconceptional sample without such biases?

Yes, but it requires more effort and resources than are usually expended in such studies. The only truly unbiased source of preconceptional data is from a cross-section of women of child-bearing age assembled without regard to their pregnancy planning status. This has been done, though infrequently. One study I am aware of drew a sample of women aged 18-24 from a register of drivers' licenses in a county and followed them until pregnancy, pregnancy loss or live birth.

An alternative which is less expensive, but which adds one small bias, is to assemble a cohort of unselected women following their first pregnancy; the likelihood of another pregnancy is highest in the few years after a first. The bias here is the absence of primigravid women. Again, whether this bias matters depends upon the research question, but I judge it to be less worrisome than the two biases noted above.

I trust the webinar will go well, and that this initiative bears fruit in the future.

Respondent 14

RE: NIH NOT-OD-21-108 "Request for information (RFI) on enhancing the science for the Environmental influences on Child Health Outcomes (ECHO) program."

I am writing in response to the above-referenced NIH RFI.

To my mind, there is no question of the vital importance of the mission of the ECHO program and the successes that already are being realized in this context. While several areas could be discussed in terms of enhancing the science in the ECHO program, I will restrict my comments here to the general issue of the Preconceptional Origins of Child Health Outcomes, and a specific proposal to support the development and testing of Personalized Just-In- Time Adaptive Interventions (JITAI) in Women of Childbearing Age.

The detrimental effects of exposure to excess stress during pregnancy on the mother and her developing child (embryo/fetus) are well established, and the development and deployment of efficacious stress reduction interventions clearly is warranted. My colleagues and I submit, based on the following considerations, that the potential benefits of interventions to prevent or ameliorate the effects of excess stress during pregnancy will be substantially greater if such interventions are implemented before women become pregnant. First, the major determinant of variation in gestational characteristics – particularly in the earliest phase of pregnancy – is the woman's pre-conceptional state. Second, the putative effects of excess maternal stress on her

developing child may be more pronounced during the first few weeks of embryonic life than during later stages of gestation. Third, by the time most women realize they are pregnant and before any measures to optimize maternal mental and physical health can be initiated (leave aside successfully implemented), substantial development of embryonic and fetal cells, tissues and organ systems may already have occurred. Hence, we focus on women of childbearing age.

While considerable progress has been made in developing interventions that are efficacious in reducing stress, current strategies for their delivery or implementation have several limitations. First, they tend to overlook population heterogeneity in terms of the effectiveness of any given intervention (the "one treatment fits all" assumption); second, their delivery in terms of time, place and context is not optimized; and third, immediate or on-going/continuous feedback has not been incorporated to adapt interventions as they are being delivered. We suggest that recent advances in sensor and mobile technology, coupled with machine learning algorithms and modern data science techniques, now engender the development and testing of personalized just-in-time and adaptive interventions (JITAI) for amelioration of stress. In contrast to traditional stress-reduction interventions that rely on the participants' recollection and implementation of stress reduction strategies in real-life stress situations, JITAIs can detect in real-life and in real-time the times and places or situations when individuals are in greatest need of an intervention, and can trigger the deployment of interventions during these times, thereby increasing the likelihood of psychological or behavioral change. The approach to deliver a stress-reduction intervention when it is most needed relies on the use of sensor-based mobile technology for ecological momentary assessments (EMA) of current cognitive, affective, behavioral and physiological states in every-day life, to which JITAIs can be tailored to participants' immediate needs and administered in real time, thereby creating an interactive and dynamic treatment strategy.

Respondent 15

Matt, my only thought about the ECHO RFI is something you are probably already considering - NIH could create a phone app that allows women to monitor their menstrual cycles and then seamlessly continue to collect information on those planning a pregnancy, getting pregnant, and delivering.

NIH is in such a good position to provide at every stage useful information on normal physiology and healthy behaviors that would motivate women to keep participating. There are already hundreds of millions of women who use commercial apps for this purpose, so there should be a ready market out there for something free, well-designed, confidential, and with health promotion and scientific research as its sole motive.

Some of the existing apps are really excellent, but all are limited in one way or another. I don't know if NIH can justify competing in this hot market with the sole purpose of education and research. A partnership with an existing company might also be possible, although with its own challenges. Full disclosure: our group is already collaborating with researchers at several app companies in the analysis of their massive data. It's a brave new world out there.

The issues are complicated - but something along these lines might be the best possible option for getting the data you seek.

Respondent 16

Dear Dr. Arteaga,

As leaders of an ECHO cohort, it has been a privilege to participate in this team science enterprise and impressive effort to engage as a community of scientists aligned in common goals of improving child health through consideration of environmental influences. On behalf of our cohort award, we are pleased to provide our comments to this Request for Information.

1. Approaches to promote scientific value while reducing burden on participants and staff in large consortia of parent-child cohort studies that involve primary data collection, including but not limited to

Innovative tools and approaches for remote data and biospecimen collection in large epidemiologic studies

The environmental exposure assessment opportunities in the program are currently based on biospecimen, geographic, or questionnaire-based measures. These approaches are not particularly strong for teasing out exposures experienced in different key indoor environments where children spend the vast majority of their time (home, school, daycare). New low burden, low-cost environmental media-based exposure assessment is possible with the advent of low-cost sensor applications which have matured greatly in recent years (e.g., Purple Air or similar low-cost sensors for indoor air assessment, Electrostatic Dust Cloth for settle dust collection).

Drinking water sampling, including private well water, is another area where the program could be enhanced, with HHEAR

Innovative blood collection procedures that allow for painless remote collection should be considered. (e.g., https://www.tassoinc.com/)

Optimal frequencies of data collection

To decrease burden on staff be conscientious about appropriate time for data asks.

Balance of essential and recommended protocol elements

Overall, the ECHO protocol is quite burdensome on both participants and staff. Some participants are faced with completing many online surveys, which take an hour or more to complete when compiled, and in-person study visits can run several hours as well. This level of burden can certainly contribute to participant drop out and/or poor data quality (missing data, skipped visits, etc.). The ECHO program helpfully distinguished essential vs. recommended protocol elements in an effort to prioritize a streamlined and lower-burden protocol that is required (i.e., “essential”) but they could have gone further in restricting the scope of the essential protocol. There are several very long and burdensome maternal surveys that are currently essential, some of them asking mothers to recall details such as brand and dosage of vitamins taking during a pregnancy over 5 years ago. The ECHO cohort is so large that it would be over-powered to answer most research questions. It may have worked well, for example, to collect certain data elements only in subsets of cohorts or participants, perhaps chosen to reflect a target population for inference, rather than having all 50,000 families attempt to complete an expansive protocol.

2. Nimbleness to address public health emergencies in large collaborative consortia of longitudinal studies

The ECHO-wide cohort communication standard is too slow to be able to move quickly in response to an emergency or public health crisis. Needing to wait 2 weeks for an ECHO communication to be approved is in direct conflict with enhancing ECHO's nimbleness. There needs to be an easier way for investigators to communicate with each other. The introduction of IdeaScale may help, but there are concerns that not enough investigators will use this platform for it to fill this important need for faster communication.

We also have challenges related to collecting data quickly over a short period of time. The typical requirements for data collection (i.e., collect once in this life stage) leads to observations that are widely spread out. If future time-sensitive needs arise, we could ask cohorts if they would like to sign on to more of a single or multiple point in time "blast" where the goal is get data on as many as possible over a short period. In other words, if we want to be nimble in response to something specific, we'll need to consider other data collection protocols. Many cohorts did this in response to COVID, but we were too slow at the ECHO- wide cohort level to organize these efforts and the individual cohorts were able to respond much faster.

3. Engagement strategies to enhance recruitment and retention of diverse study populations

Need to prioritize PIs who are from the communities ECHO hopes to recruit from, this would both enhance diversity in leadership and provide insights and trust required for success.

To a significant degree, this is an empirical question. Effective retention and engagement strategies need to be systematically developed and evaluated. The ECHO program could dedicate funds, for example through the OIF mechanism, to encourage empirical tests of different strategies followed by sufficient resourcing to rollout "evidenced-based" (supported) strategies for implementation by cohorts to better reach targeted study populations. Importantly, engagement and retention are separate considerations. Whereas certain strategies may apply to both efforts, work is needed to develop and evaluate strategies that are uniquely suited to each.

Long-term retention is a significant (and costly) consideration, yet selective attrition is a major threat to the validity of longitudinal findings. ECHO could support working groups designed to dedicate significant attention to developing a toolkit of tools (e.g., recommended online location services) and strategies for cohorts to implement. Significant, set-aside resources are needed for retaining participants, especially diverse participants, over extended periods of time with not only financial incentives but other creative efforts.

4. Promotion of diversity in the scientific workforce related to child health:

The few early career investigators who meet underrepresented category are saturated with work (i.e., the minority tax). Programs such as the ECHO Supplement to Promote Diversity need to offer support earlier in the pipeline. Examples could be providing funding for student internships, RA positions for graduate students, etc.

ECHO program and core leadership should be more diverse; the extant Cohort PIs are also not as diverse as they could be and this constrains the pool from which leaders are pulled; efforts should be made to invite and cover the time of leaders from underrepresented backgrounds to join ECHO teams.

A formal mentoring program could be implemented that is directed toward pairing senior investigators with promising early-career scholars from under-represented backgrounds with a systematic, staged work plan that helps scholar work toward independence as investigators.

5. Preconceptional Origins of Child Health Outcomes:

As ECHO children age, ECHO should not discount the value of examining exposures and outcomes throughout the life course, including later in childhood, adolescence, and through adulthood. Environmental epidemiology focusing on the adolescent period is scant, despite the unique and important changes in exposure and organ system growth and functional development in this period. The adolescent period is also when the incidence of some of the neurodevelopmental outcomes with very high public health burden (e.g., depression) increase rapidly.

Attention to exploration of intergenerational exposures and outcomes related to current ECHO participants might be more compelling and feasible than expanding ECHO's aims to preconception.

The National Children's Study attempted to collect pre-conception data. It may be instructive to carefully study this effort and its successes and issues related to pre- conception research, specifically.

6. Other topics

To achieve ECHO's goals of producing impactful science, ECHO needs people at the national level who are focused on designing concepts and analyses using the end products from the SPLAT and End-User Stakeholder groups. Ideally, cohort investigators with a deep understanding of ECHO would be elevated and compensated to facilitate these "connection moments" where ECHO science responds to the stakeholder community needs. ECHO could budget at the national level or at the cohort levels for a "Stakeholder Science Liaison" whose job it is to coordinate responses.

Funding is needed to adequately cover Investigator time to lead working groups and take on other ECHO leadership roles. This protected time could enhance ECHO's ability to respond to public health crises more rapidly and allow for time to address emerging science needs (analyzing extant data to answer questions and designing new data collection to learn what is needed, as in the case of the COVID-19 pandemic) and to working with stakeholders to translate the science for use.

The ECHO process has resulted in many unanticipated asks from currently involved cohort PIs, Investigators and Staff. Potential grantees should be encouraged to allot sufficient FTE for ECHO-wide efforts.

SPLAT force should be reinstituted.

There needs to be more careful thought devoted to whom ECHO study results generalize. Given that we are a cohort of cohorts and that there was no systematic sampling strategy implemented across components (with some cohorts oversampling for specific outcomes), the "ECHO sample" does not have a well-defined target population. Thus, asking questions about prevalence/incidence of anything within ECHO is mostly meaningless from a generalizability perspective. There are methods we can consider to deal with issues that do not require having perfect knowledge of the sampling strategy to implement (i.e., raking). These are strategies we should consider implementing broadly if our goal is to generalize to children in the U.S.

Respondent 17

Dear ECHO,

There is increasing discussion about data libraries and languages and harmonizing data elements to facilitate data sharing. We need to enhance our efforts to standardize our collection of data on the 'environmental' side of environmental health. The expertise to do so may lie outside the EH research realm (e.g. NSF, EPA, env. engineering, housing professionals and organizations like the National Center for Healthy Housing).

ECHO has learned much that could inform simple, basic and realistic ways of characterizing environmental exposures in biomonitoring cohorts to support future analyses. I often wonder how much further we could move toward causes and actions with what we learn from these cohorts if we had basic housing and occupational data, or even zip codes to include in the analyses...but we don't!

For example, are you now pushing out 'geomarker' collection/characterization guidelines for future/ongoing cohorts? Or 'top 3' questions to ask about housing?

There may also be a key role for the private sector: Have you reached out to EPIC and other EMR companies re: how they collect/store SDH info? Conversations with our EMR team (in a DEI context) have made it clear that EPIC's decisions about how to allow/promote SDH information collection are crucial to clinical research. Individual 'users' like one University at a time can't impact them, but I would imagine offering your expertise and role as a key data user could impact them effectively.

Finally, the use of outdoor (even fine scale) air measurements for these analyses continue to baffle me, given the observation that people spend so much more time inside their home than out. I know the BU/Harvard group has done some nifty things by using housing age and heating source to modify outdoor air pollution, but that seems rare.

Respondent 18

To whom it may concern,

RE: NOT-OD-21-108: Request for Information (RFI) on enhancing the science for the Environmental Influences on Child Health Outcomes (ECHO) program

I am writing in response to the above RFI; I am a PI on one of the ECHO cohorts and have some insight into the nature of the program and its standing in the field.

There is no question that the ECHO program is the leading US strategy for understanding how early exposures may have life-long consequences for health outcomes, the factors that moderate risk, and the resulting strategies that may improve health outcomes for the population. The concept that there are "early exposure" effects on health outcomes is not new, but the diversity (and non-reliably) of reported findings is, frankly, a significant concern. In that context, the strategies and logistics of the ECHO program are the needed and necessary responses because they sidestep the problems of numerous and unnecessarily contrasting approaches to answering a clinical or public health question. We do know that there has been quite limited success in promoting health and the science of health. Programs like ECHO are designed to improve the rigor and impact and relevance of research for promoting child and family health. In this age of

limited public understanding of science, sometimes accompanied by actual resistance to science, it is essential that the US have go-to, high-profile, and impactful programs of study. The ECHO program is that, and it is the leading effort for understanding child health, a crucial national concern. Furthermore, given that the standard program model (i.e., R01) budget has not changed in many years, any individual R01 will be severely limited to make a significant impact – especially so in terms of public health significance. That means that the ECHO program can provide the sort of guidance and firm scientific foundation for decisions concerning the health of children and families.

The specific matter of pre-conception origins of health is an important topic, and requires additional interest and consideration. It needs to be considered alongside the already well-established prenatal origins of child health, for which we already have an abundance of evidence and opportunities for health promotion. We do not yet see sufficient application of this strong knowledge base, however. What is needed now are efforts to emphasize, for the purposes of public health and public understanding of health, that health begins before birth. While those efforts are in full swing, efforts to build and extend the scientific basis for pre-conception origins of health would be valuable.

Respondent 19

Information Requested

This RFI seeks input from stakeholders throughout the extramural scientific community and the general public regarding enhancing the science of ECHO.

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

I. General Topics

- Approaches to promote scientific value while reducing burden on participants and staff in large consortia of parent-child cohort studies that involve primary data collection, including but not limited to
    - Innovative tools and approaches for remote data and biospecimen collection in large epidemiologic studies
    - Optimal frequencies of data collection
    - Balance of essential and recommended protocol elements
- Nimbleness to address public health emergencies in large collaborative consortia of longitudinal studies
- Engagement strategies to enhance recruitment and retention of diverse study populations
- Promotion of diversity of the scientific workforce related to child health

We strongly recommend that the ECHO NIH Program staff solicit and carefully consider input from cohort PI's about how to reduce burden on participants and staff. Those who are conducting the EWCP in their cohorts will have the best advice on what aspects are too burdensome for participants or staff. This will likely differ by life stage.

Instead of the current protocol where there are a large number of essential elements and cohorts do not have the flexibility to add recommended elements, we suggest relatively few essential elements that can be collected successfully from all cohorts without creating undue burden, and a

requirement that cohorts do a certain percentage of the recommended elements based on the focus, interests and expertise of their individual research groups. We believe this will lead to a higher quality dataset.

II. Preconceptional Origins of Child Health Outcomes:

- Identifying solution-oriented ("so what") scientific questions about preconceptional origins of child health outcomes, based on knowledge from pre-clinical, clinical work, and population research, including but not necessarily limited to the following preconception factors:
    - Obesity and lifestyle factors such as diet, sleep, physical activity
    - Physical and chemical exposures
    - Fathers
    - Psychosocial and societal influences

We recommend that ECHO NOT be expanded to include a preconception arm. While preconception factors are vitally important and understudied, preconception studies are challenging to conduct and very resource intensive. Given how large and complex the ECHO Program already is, we feel it would be very difficult to implement a preconception arm successfully while at the same time successfully retaining and following the already assembled cohort. A considerable increase in funding would be needed to add a pre-conception arm without jeopardizing the future success of the existing cohort that ECHO has spent 7 years establishing.

- Strategies for recruiting participants preconceptionally, and retaining through pregnancy into childhood
    - Feasibility of different strategies, including ensuring adequate sample sizes of births and participant diversity, from
    - Young women and men, already participating in ECHO cohort studies, entering reproductive age
        - Women with a recent pregnancy in ECHO, and their partners, who may have a subsequent pregnancy
        - Women and men of reproductive age irrespective of previous participation in ECHO
- Measures and biospecimens from prospective mothers and fathers that cohorts should collect prior to or in early pregnancy, including among the 3 sources of potential participants above
- Ethical considerations regarding study participation of biological and non-biological fathers

Should a pre-conception arm be added this could be done most successfully within the context of ECHO by recruiting women already enrolled in ECHO but planning a subsequent pregnancy, or children enrolled in ECHO who have reached reproductive age. We do not think it would make sense or be cost effective to recruit new pre-conception cohorts for inclusion in ECHO.

Respondent 20

Hello –

Overall, we recommend that NIH put most of its resources going forward into maintaining and following the children already enrolled in the ECHO cohort. The investment in ECHO has been substantial with an enrollment goal of over 50,000 children and their families and over 50% representation of non-white participants. We recommend that any additional funds be devoted to increasing participation in ECHO among under-represented groups.

I. General Topics

Regarding reducing burden on participants and staff: we strongly recommend that there be a thorough evaluation conducted to identify lessons learned from implementation of the ECHO Program and its predecessor the National Children's Center Study. The evaluation should identify, discuss and share best practices used to reduce challenges. We also strongly recommend that the ECHO NIH Program staff solicit and carefully consider input from cohort PI's about how to reduce burden on participants and staff. We recommend that funds are invested in all current ECHO participants and following those already enrolled and engaged in the program over time.

We recommend a substantial planning period with priorities and policies determined early-on to reduce burden on staff and participants. Databases should be set up prior to the start of data collection in all languages applicable to the study populations at all sites. For example, to reduce participant burden and help with retention, all surveys should be available online in all applicable languages with the ability for participants to save progress and return later to complete. In addition, goals and metrics used to measure progress should be discussed and determined prior to the start of recruitment, enrollment, and data collection.

Regarding optimal frequencies of data collection: ideally all sites would follow-up a similar visit schedule. We recommend tightening the parameters of the visit windows. For example, the middle childhood visit window is 6 years long. Dividing this up into middle childhood 1, 2, 3, etc. would help to calculate data completeness over time. To assist with retention, we recommend visits happen at least once yearly.

To assist with recruitment and retention of a diverse study population we strongly recommend that study materials are written at an accessible literacy level and that translation of data collection forms and other study materials into languages other than English be a high priority. Further, we suggest ultimate flexibility in enrolling diverse study populations, including allowing for in-person or remote data collection, grace periods for biospecimen and data collection, and adequate resources to assist on-the-ground staff in reaching out to and establishing rapport with diverse communities, including sufficient stipends to reimburse for time and contributions to the study. Finally, we recommend specific funding for community engagement efforts across all cohorts.

Regarding balance of essential and recommended protocol elements: we recommend a minimal number of essential measures or measures that must be completed across all cohorts. We suggest a small number of targeted measures that would only be implemented at sites recruiting populations of interest to those measures. We believe this will lead to a higher quality dataset. In addition, we suggest utilization of Computer Adaptive Testing (CAT) whenever possible to improve data collection efficiency and reduce burden on participants and staff.

Regarding promotion of diversity of the scientific workforce: we recommend continuing diversity supplements.

II. Preconception Origins of Child Health Outcomes

We recommend that NIH put most of its resources going forward into maintaining and following the children already enrolled in the ECHO cohort. The investment in ECHO has been substantial with an enrollment goal of over 50,000 children and their families and over 50% representation of non-white participants. We recommend that any additional funds be devoted to increasing participation in ECHO among under-represented groups, for example expanding efforts to include different Asian groups such as Southeast Asians and South Asians.

Preconception studies are very challenging to conduct and very resource intensive and would be very difficult to successfully implement within the large and complex framework of ECHO without a large influx of new funds for research and infrastructure. If NIH is strongly committed to adding a preconception arm, then we recommend it would be through additional pregnancies of women already enrolled in ECHO or children already enrolled in ECHO that are reaching reproductive age. Finally, a thorough evaluation and reexamination of the National Children's Center Study to determine how to strategically enhance preconception collection and the continuation of the ECHO Program is strongly recommended.

Respondent 21

Dear Dr. Arteaga,

I am writing to respond to several of the "General Topics" listed in the RFA including reducing participant burden while enhancing recruitment and retention of diverse study populations.

One way to enhance recruitment and retention of diverse study populations is to reduce participant burden. When you over-burden participants, retention rates go down, and this is amplified in populations that have already over-burdened lives—populations subgroups including those with lower income or lower education or BIPOC--the very disadvantaged populations for whom we're aiming to increase enrollment and retention rates!

A pubmed search of "longitudinal participant retention" gives 1,151 hits. I include a few highlights below.

1. "Results suggest that strategies that aim to reduce participant burden (e.g., flexibility in data collection methods) might be most effective in maximising cohort retention." Teague S, Youssef GJ, Macdonald JA, Sciberras E, Shatte A, Fuller-Tyszkiewicz M, Greenwood C, McIntosh J, Olsson CA, Hutchinson D; SEED Lifecourse Sciences Theme. Retention strategies in longitudinal cohort studies: a systematic review and meta-analysis. BMC Med Res Methodol. 2018 Nov 26;18(1):151. doi: 10.1186/s12874-018-0586-7. PMID: 30477443; PMCID: PMC6258319.

2. "Of 1281 eligible women, 744 were enrolled (58% recruitment rate); retention rates were 87%, 70%, and 55%, respectively, 2 weeks and 3 and 6 months post-intervention. Being unmarried, younger, and having low baseline vegetable intake predicted loss to follow-up." From: Di Noia J, Schultz S, Monica D. Recruitment and retention of WIC participants in a longitudinal dietary intervention trial. Contemp Clin Trials Commun. 2019 Sep 6;16:100438. doi: 10.1016/j.conctc.2019.100438. PMID: 31535056; PMCID: PMC6744523.

3. "Retention rates ranged from 39%- 41%. Retained participants tended to be older and female. In age- and sex-adjusted analyses, retained participants were more educated, single, and in better

health status than those not retained." From: Holt CL, Le D, Calvanelli J, Huang J, Clark EM, Roth DL, Williams B, Schulz E. Participant Retention in a Longitudinal National Telephone Survey of African American Men and Women. Ethn Dis. 2015 Spring;25(2):187-92. PMID: 26118147; PMCID: PMC4593062.

4. " Consistent with prior research, higher retention rates were found among Whites, females, and married individuals as well as those with better health and more education." From: Radler BT, Ryff CD. Who participates? Accounting for longitudinal retention in the MIDUS national study of health and well-being. J Aging Health. 2010 Apr;22(3):307-31. doi: 10.1177/0898264309358617. Epub 2010 Jan 26. PMID: 20103686; PMCID: PMC2837791.

One suggestion is to have a VERY STREAMLINED core protocol that includes biospecimens plus a minimum set of outcome assessment for all 5 ECHO outcomes and then have more detailed protocols for each of the 5 ECHO outcomes that cohorts could opt into. This would be analogous to how a single cohort study might attempt to collect their core protocol on all participants but then offer participants additional incentives to opt into ancillary studies.

Respondent 22

Dear Dr. Sonia Arteaga:

Thank you for extending the deadline for the ECHO RFI. Please find brief comments below for the two RFI sections, also noting that these suggestions are my own and are not intended to represent any affiliated institution or program.

I hope that some of the strategies or recommendations prove useful.

I. General Topics

Approaches to promote scientific value while reducing burden on participants and staff in large consortia of parent-child cohort studies that involve primary data collection:

The ECHO program might benefit from hosting an annual virtual forum that specifically highlights innovative tools and approaches for remote data and biospecimen collection in large epidemiologic studies. As an example, cohorts such as the Safe Passage Study (PASS) Cohort are implementing novel remote blood collection protocols that might be vetted for approval to use ECHO-wide.

Cohorts can be encouraged or provided tools and resources to collaborate with institutions and scholars who are engaged in community-based participatory research, primarily for continual engagement and feedback to enhance recruitment and retention of diverse study populations. Doing so might additionally impact your interest in understanding of optimal frequencies of data collection, balance of essential and recommended protocol elements, and nimbleness to address public health emergencies in large collaborative consortia of longitudinal studies.

ECHO can partner with the Office of Scientific Workforce Diversity and the NIH extramural research community for strategic and targeted efforts to recruit and retain a diverse scientific workforce related to child health, also working closely with the NIH UNITE Initiative.

II. Preconceptional Origins of Child Health Outcomes:

Identifying solution-oriented ("so what") scientific questions about preconceptional origins of child health outcomes, based on knowledge from pre-clinical, clinical work, and population research, will benefit from a strong focus on the role of structural racism and the implications of persistent residential segregation. Structural racism may relate to or potentially undergird potential disparities in all the factors listed in the RFI including: Obesity and lifestyle factors such as diet, sleep, physical activity; Physical and chemical exposures; Fathers; and Psychosocial and societal influences.

ECHO might also consider coordinating data collection and research efforts with the All of Us Research Program and other diverse and established cohorts, e.g. the Black Women's Health Study (BWHS) or PRIMERO (Puerto Rican Infant Metagenomic and Epidemiologic study of Respiratory Outcomes).

I very much look forward to attending the workshop on Preconceptional Origins of Child Health Outcomes on June 17-18th -- if possible, it would be great to have another opportunity to submit additional feedback following this event.

Thank you,

Respondent 23

Hello,

I am writing to provide feedback about NOT-OD-21-108. I am a researcher at a university (and a current ECHO cohort PI).

Feedback was requested about the balance of essential and recommended protocol elements. Based on ECHO experiences to date, I strongly recommend that cohorts that are selected for this opportunity are given information about the approximate duration of essential protocol elements, and the timing of the assessments, in advance of the NOSI/RFA submission deadline. Some of the challenges in the current ECHO project are due to this information not being yet known when teams were initially applying to be part of ECHO, and thus diverse expectations were held by cohort awardees. If it could be clear in the published RFA what would be expected in terms of the duration/quantity of essential and recommended elements, I think this would facilitate quicker and greater alignment between cohort awardees and program/coordinating center staff, which would expedite the launch of the protocols.

Data collection approaches/methods that can be done remotely would enable a more diverse set of participants to be reached for ECHO. Requiring intensive in person assessment biases the sample to those in health care settings and/or in major cities, and makes it less likely that participants in rural areas will join ECHO.

I greatly appreciated the recognition of fathers in this RFI. Not only do fathers contribute genetic material to their offspring, their own health and environmental circumstances can contribute to their reproductive health, which can affect sperm and then fetal development prenatally. In addition, the role of fathers postnatally is important. Yet, our science around the contributions of fathers lags significantly compared to that of mothers.

In terms of strategies for recruiting and retaining participants – for those already in ECHO, or new participants considering ECHO – I have a suggestion. If a standard set of core questions could be developed into a 10-minute survey that is given as soon as it is known that a participant

is pregnant or attempting to conceive, this could yield some excellent prospective data that could begin to be collected even before ECHO2 is launched (and then, these data could be incorporates into ECHO2 as extant data).