

## Expert Panel Meeting on the Design of a Longitudinal Study of the Impact of Prenatal Opioid and other Substance Exposure on Brain and Behavioral Development

### Meeting Summary

#### Background

On October 22, 2018, a panel of experts was convened to inform the development of a trans-National Institutes of Health (NIH) initiative that includes the National Institute on Drug Abuse (NIDA), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Institute of Mental Health (NIMH), the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Minority Health and Health Disparities (NIMHD), and the NIH Environmental Influences on Child Health Outcomes (ECHO) program.

The goal of the meeting was to discuss study design and bioethical issues critical for conducting a large-scale longitudinal study on brain development from fetus to childhood, as well as on the effects of prenatal and postnatal substance exposure and adverse environmental conditions on the developing brain and related cognitive performance and behavior.

The charge to the expert panel was given by the Directors of NIDA, NIAAA, NIMH, and the ECHO program.

Following the charge to the panel was a summary of the [first expert panel meeting](#) held on September 24, 2018. That meeting covered the developmental effects of prenatal substance exposure; measurement of fetal/neonatal brain development and growth; measurement of pediatric brain development; and early childhood cognitive, social, and emotional development assessments.

The second expert panel meeting focused on three major areas:

- Bioethical, Legal, and Social Service Considerations
- Longitudinal Study Design
- Recruitment and Retention

The agendas and summaries from both expert panel meetings can be found under “Understanding Consequences of Prenatal Opioid Exposure on Brain and Behavioral Development” [on this page](#).

#### Session 1. Bioethical, Legal, and Social Service Considerations

The bioethical and legal considerations were brought up first, as they are considered critical to the concept and design of a study that may begin prenatally and include the study of illicit substances.

Several foundational issues were raised, including concerns surrounding mandated reporting, certificates of confidentiality, and the treatment of the mother-baby dyad and family unit.

## Foundational Issues

- [According to U.S. federal guidelines](#), in studies *without* the prospect of direct benefit, the risk to the fetus (or to a child) must be no greater than minimal, and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means.
- Pregnant women who use substances or who live in adverse conditions are at an increased risk of certain negative outcomes, including:
  - Legal—Loss of custody, incarceration, and criminal charges
  - Social—Partner violence, stigma, bias, blame, shunning by family and community
  - Psychological—Feelings of self-loathing and guilt
- Conducting a study with pregnant women, some of whom use substances, will require consultation with representatives from pregnant women’s advocacy organizations, Child Protective Services (CPS), law enforcement, and legal advocates to determine how to mitigate these risks.
- Learn from mistakes made in previous research on prenatal substance exposure, including how findings are interpreted and disseminated to policymakers and the public.
  - During the crack epidemic, poorly controlled research (i.e., not accounting for poverty, interpersonal violence, other adverse environmental conditions) led to inappropriate conclusions and fostered negative stereotypes and harmful policies.
- Consideration should be given to the ethics of conducting an observational study in populations with limited access to appropriate prenatal care and/or addiction treatment
  - Are there direct benefits that the study can provide without inclusion of an intervention?
  - Can linkage to services be provided?
  - In a multisite study, how can the variability in availability of resources/services across sites be addressed?
- May want to consider restrictions on participation, such as only including:
  - Mothers using legal substances (e.g., tobacco, alcohol, medical use of prescription opioids), though this doesn’t necessarily exclude them from risk of prosecution and imprisonment in some states.
  - Pregnant women who have already been identified with a substance use disorder (SUD) or are in treatment.

## Messaging

Messaging the goals of the study will be crucial from the beginning. A communications plan and team are essential.

- Ensure messaging is clear about resilience as well as risk so as not to stigmatize exposed children and create self-fulfilling prophecies.
- Identify the focus on typical development as a major goal. This may also help with recruitment efforts.
- Focus on identifying the broad range of factors that contribute to risk of harm or to resilience in the face of early life adversity. Avoid language blaming maternal (or paternal) behavior.

- Focus on the potential benefits of the study:
  - To inform how and when to intervene during pregnancy and postpartum to improve health outcomes for mother and child.
  - To develop best practices for infants with neonatal abstinence syndrome (NAS) (e.g., rooming in, breastfeeding).
  - To transform the way we treat the mother-baby dyad.
    - Shifting the focus to the mother-infant pair
    - Reducing negative biases by emphasizing the biological and societal underpinnings of SUDs, and its responsiveness to treatment.
  - To systematically examine the impact of CPS involvement on mother/child/family. For example, is there a greater risk of relapse in a mother that loses her child to CPS? *This may be beyond the scope of the study.*
  - To understand how to mitigate risks to the population.

### Informed Consent and Mandated Reporting

- Certificates of Confidentiality (COC) protect investigators conducting research from disclosing identifying information to any court or other person not connected with the research. However, this protection does not extend to disclosure required by Federal, State, or local laws.
- The Safe Passage study in South Dakota, where use of alcohol during pregnancy is a reportable offense, established a memorandum of understanding in which the state would provide a waiver from mandatory reporting. This meant that the researchers and clinicians were not required to release personally identifiable information on any individual.
  - Some concern about whether this would hold up if state officials changed.
  - Some agreements are negotiated with permanent employees, rather than elected officials, to ensure continuity.
- Negotiate on state-by-state basis, although state laws may change over the course of the study. Participation in some states may not be feasible if appropriate precautions cannot be achieved.
- Seek input from study teams. Nurses/social workers/school teachers may have their own ideas about mandatory reporting.
- Work with CPS.
  - CPS is often triggered by Medicaid involvement, so there is a disproportional impact on low-income mothers.
  - There is a risk to the mother and child if the child is returned to the mother following removal and the mother relapses.
  - Institutional Review Board (IRB) requirements (e.g., state/local IRBs when children enter CPS).

### Role of the Biological Parents in the Study

- Respect for the biological mother as a study participant, not merely as a vessel for the child.
  - Include measures for the mother/parents.
  - Measure what they are doing right.
  - Ask substance-using participants about barriers to stopping use.
- Maintain parental involvement if the child is removed from parental custody. Continue to offer access to services where possible.

- Other issues to consider for the mothers/families:
  - Multiple psychosocial, medical, and life (e.g., jobs, childcare) stresses.
  - Mothers may be facing a lot of intervention—court-mandated services, substance abuse treatment.
    - How to account for the fact that some mothers and children will be going in and out of treatment or other services? Compliance needs to be monitored.
    - Need large enough sample to accommodate these factors.
- Need to balance risk to the mother (legal consequences) with risk to the safety of the infant and/or other children that are in the mother’s custody.

## Session 2. Longitudinal Study Design

It will be very important to consider the discussion from Session 1 in designing a study that balances the risk of participation for dyads and families/caregivers with potential benefits to them.

- What is the overall framework for the intent of the study?
  - Without understanding the trajectory of normal brain development, we cannot understand the effects of adverse childhood experiences (ACEs) and substance use on normal brain development, and we cannot know when and how to intervene.
    - Within the context of normative development, strive to understand the effects of prenatal substance exposure and exposure to other adverse or therapeutic experiences.
    - Must also assess how supportive environments alter development trajectories, determining which factors contribute to resilience in the face of early adverse experiences.
- What exposures should be included?
  - The most common exposure will be alcohol. According to a [Centers for Disease Control and Prevention Vital Signs report](#), about 3.3 million women in the United States are at risk for an alcohol-exposed pregnancy.
  - Non-substance use–related ACEs may have a greater impact than substance exposure. Design the study with adequate controls for environment and ACEs. Consider the broader context of poverty, abuse, and other relevant social and environmental (e.g., lead) factors.
  - Need a clear definition of what constitutes exposure to opioids.
    - Prevalence of use—Does any use of opioids count? Some minimum threshold?
    - Include exposure during management of pain.
    - Include those on opioid agonist therapy.
  - Timing is critical—Exposure during some developmental periods may have different effects than others. What are the implications of this for sampling strategy?

### Study Design Considerations

- Prospective longitudinal design, other designs?
  - The consensus was that a prospective longitudinal design is the best approach.
  - Can’t do a national probability sample but can seek a diverse sample to address external validity to varied populations.

- Consider siblings in a fixed-effects model, especially if there is a disparity in substance exposure (or other critical variables).
- Representative versus catchment areas
  - It is not feasible to have a nationally representative sample of the population. The study will be driven by centers that can do the imaging, as well as state and local laws.
  - Make efforts to capture all pregnant women within catchment area, multiple sites within catchment area (using Census and epidemiology studies) to capture diversity. Focus targeted efforts to identify pregnant women within it.
  - To address socioeconomic balance, consider a rural catchment area with variability in it. We want to have diversity across catchment sites in terms of economics and race/ethnicity. We want to cover the strata from heavy to light/nonusers, but also want a diverse population achieved by multiple sites and multiple catchment areas.
- Include range of exposures:
  - Early use and quit
  - Early use and continued
  - Identified at birth
- Timing of enrollment
  - Focus on prenatal identification—Critical information that will inform trajectory.
  - Recruitment at birth could be a complimentary approach.
  - Useful to have a hybrid design (time of birth and during pregnancy).
  - Boston Birth Cohort—During pregnancy or at birth, do not recommend preconception recruitment.
- Duration of enrollment—The opioid epidemic is rapidly evolving. Minimize recruitment time to ensure a similar type of drug exposure, as preferred opioid, potency, and prevalence can change drastically in a short period of time.
  - In contrast, staggered enrollment would give sites chance to get up and running. It could also provide an opportunity to evaluate changes in treatment options, maturation, and other local context factors that change over the course of enrollment.
- Duration of study
  - Does the study need to follow children to age 10 to answer relevant research questions? Would infancy to 3-5 years old be sufficient? Or until school-age?
    - It would be good to go until the age at which the Adolescent Brain Cognitive Development (ABCD) study begins assessing kids (9-10 years old) for continuity and to accomplish the goal of creating a comprehensive compendium of development from birth to young adulthood.
    - It would be good to harmonize with ECHO and ABCD.
- Planned missingness—A design strategy in which the core variables of interest are captured on the entire cohort while detailed exposure assessment information is collected on a specially selected subset of the study population.
  - It could be used, but it requires careful implementation to ensure statistically valid data. The validity of its use depends on the number of research questions.
  - Planned missing design works if you have high correlations within measures across time points but is problematic if that assumption is not met.

- Additional assessments to consider:
  - Early language development—One of the best indicators if child is on track related to frontal cortex development.
- Learn from other studies, such as:
  - The Early Childhood Longitudinal Study, Birth Cohort
  - Boston Birth Cohort
  - Safe Passage study (South Dakota)
  - National Children’s Study
  - Baby Brain Connectome Project
  - Families First
  - Fragile Families

### Sampling Considerations

- Number of sites
  - A few larger sites with internal diversity is easier to manage than many smaller, nondiverse sites.
  - If sample is 10,000 at 20 sites, that is 500 participants per site, which is a large burden.
  - Identify sites by prevalence of opioid use/abuse (concentrate on Appalachian region?).
    - Need to be sure that there are more than one or two sites that are enrolling high-risk participants so that losing individual sites does not compromise the whole study.
- Diversity
  - Diverse set of sites, spread nationally, in both urban and rural communities, will help to avoid clustering effects and improve external validity of findings.
  - How do we address the wide variability in drug use (substance/polysubstance, frequency), race/ethnicity, socioeconomic status, education, and more?
    - Need to ensure controls are from the same population as substance exposed; must avoid confounding SES, race, and exposure.
    - Build in the confounding variables as part of what we’re studying, by having adequate power and sample size to address these variables independently and/or by using complex statistical methods.
  - Target areas that are more significantly affected by high prevalence of drug use and cast a wide net to get a large number who are substance using or exposed without targeting specific groups of people.
- Considerations for determining appropriate sample size
  - Selectively target those using substances or target the general population and invariably getting some with substance use exposure? Lack of statistical power could be issues with the latter.
  - Target areas of the country with high rates of fetal exposure to substances.
  - Prevalence of substance exposures
    - What is the probability of getting 20% opioid users?
      - Boston Birth Cohort—8,500 mother-baby dyads; 281 babies with NAS (3.3%). 5-10 times higher than national data but focused on target area with high prevalence of use. Polydrug use very common. Among babies

born with NAS, about 80% of moms reported using depressants (benzos, opioids, etc.), 80% use stimulants (caffeine, cocaine), and 84% use marijuana. (Didn't calculate alcohol and tobacco.)

- Effect sizes for outcomes of interest, e.g., brain development
  - John H. Gilmore at University of North Carolina at Chapel Hill has a large data set with neonatal imaging that can inform expected effect sizes at different developmental stages. This can inform power calculations.
- Multiple modifying/moderating factors—Increases needed sample size.
- Based on preliminary power calculations (see appendix), a total cohort of approximately 8,000-10,000, oversampled for substance exposures, may meet the study objectives as currently defined.
- Need to balance sample size, frequency of imaging (and participant burden), and budget.

### Site Requirements

- Pre/postnatal research experience
- Neurological/psychological/developmental/imaging expertise
- Engagement, recruitment, and retention of high-risk populations
- Ability to manage high-throughput recruitment early in the study
- Matching of research expertise and service infrastructure in same geographic location
- Ability to form partnerships with critical stakeholders

## Session 3. Recruitment and Retention of High-Risk Populations

It's important to establish a good rapport from the moment you meet the study participant, since this is expected to be a long-term relationship. This looks very different than mass enrollment. The value proposition (i.e., benefit to the participant) needs to be clear.

### Methods for Recruitment

Ideas for recruitment venues include:

- Households
- Home visit programs
- Opioid treatment programs
- Provider/hospital-based approach—NICUs, pediatricians, OB/GYNs, psychologists, etc.
- Community based:
  - Faith-based institutions/churches
  - Vape shops
  - Laundromats
  - Alcohol Beverage Control (ABC) stores
  - Birth centers
  - Schools (early Head Start, Head Start, etc.).
  - Infants and toddlers/early intervention programs
- Social media

## Recruitment Strategies

- Tips and techniques
  - We need the support of places we're recruiting through. Referrals from health care providers and other organizations are significantly more effective than posters or advertisements.
    - There must be something in it for providers and agencies that are partnering. Giving them general aggregated (de-identified) data has been effective, or local aggregated data. They can use the data to help get grants (or state funding), etc.
  - If you create a good culture around the study, participants can become best recruiters.
  - Best source of non-exposed control group is other births at the same hospital.
  - Women engaged in Medication-Assisted Treatment (MAT) or taper are more likely to engage in studies than those who are using continuously.
- Concerns
  - Undocumented mothers and families are unlikely to participate in a study.
  - Twins? Higher percentage from assisted reproduction. May be difficult to selectively recruit.
  - Hard to enroll if not getting care. Women using illicit substances are less likely to get care.
- How to incentivize participation: what's reasonable and ethically possible? One of the major benefits may be connection to assistance programs.

## Participant Engagement

- Good team training
  - Very sensitive around language. Person-first. "Where do you stay?" (better) versus "where do you live?", not discussing a life partner or wearing wedding ring, etc.
  - Give staff motivational interviewing and sensitivity training. Have huddles around where the team is doing well and where the team can improve.
  - It is critical to have a project manager that knows your participants and can communicate well with them.
  - Recruit research assistants (RAs) with lived experience (CPS, SUD treatment, etc.)
- Referrals and access to services. Partner with different groups providing services. Need to be mindful of lack of resources for these organizations compared to research study. May even have as subcontractors depending on role. Examples include:
  - Health Resources and Services Administration/Substance Abuse and Mental Health Services Administration programs
  - Health service providers, postnatal care (pediatric, satellite services)
  - Social services
  - State and local government (e.g., WIC, SNAP, early childhood intervention)
  - Substance use treatment programs; treatment programs where mom and children can stay together
  - Tutoring/mentoring programs
  - Vouchers and subsidies (matching vouchers to leverage WIC/SNAP at farmer's market, child care subsidy vouchers, access to subsidized housing)



- Enable them to improve the quality of care for their children; may also help with CPS to keep families together
- It will be essential to not only engage the decision makers in the various agencies, but to also cultivate relationships with the “middle managers,” the cadre of folks that are stable in the agencies regardless of the political leadership.

## Retention

- Tips and techniques
  - Make strong efforts to maintain staff long term. Participants will feel much more comfortable interacting with the same staff member(s) throughout the study.
  - Explore the idea of giving the women the chance to know each other and form a peer support group. Allow them to be part of a cohort. MAT can be like moms’ groups, and birth outcomes are better. Moms could talk to each other outside of study. Form a personal relationship with others going through it.
  - Be willing to go to where they are.
  - Have a flexible design.
  - Provide a range of accommodations that will make it easy for participants to stay engaged:
    - Car services for transportation to and from local appointments; flights and hotel for longer distance sites.
    - Child care during appointments if they have other children.
  - Make use of tools for maintaining contact:
    - Pre-paid cell phones
    - Birthday cards
    - Access to medical or Medicaid database
    - Lots of alternative contacts as time goes on—Up to eight sometimes.
  - Stay visible in community—Feature logos prominently with institutions, etc.
  - Keep the community resources updated—Do warm handoff.
  - Create an RA cheat sheet—Kid name, birthday, anecdote. Positive environment.
  - Use Electronic Medical Records (EMR) to track when/where mom or baby come for primary care appointments or specialist appointments. Line up study visit with their medical visit to minimize burden. Also obtain pertinent medical information. Minimize cost.
- Concerns
  - Follow-up rates vary based on risk groups. The ongoing Perinatal Imaging of Neural Connectivity Study has seen do not call rates between 5-20%, with slightly higher rates in substance users. Mental health and trauma were different across the board, with more trauma in substance users. The ability to see co-morbidities and to follow participants will vary.

## Conclusion

The focus of this meeting was on legal, ethical, and social service issues, recruitment and retention of high-risk populations, and additional study design concerns (sampling strategy, size, diversity). Great

care will need to be taken to minimize harm, given the intent to enroll, in part, a disadvantaged and stigmatized population. A careful experimental design with thorough considerations for the well-being of the mother-baby dyad and special protections may help mitigate the risk to participants. Ideally, this study will focus on advancing the understanding of normative brain development from prenatal to prepubescent stages of life, while incorporating diversity in socioeconomic status, race/ethnicity, education, and early life experiences, such as ACEs and substance exposure, to identify factors that confer resilience to adverse experiences and can improve outcomes. Providing assistance in the form of early detection of problems and connections to services for high-risk participants may facilitate the benefit to participants and society.

## Appendix

### National Children's Study Resources

- [National Children's Study Overview](#)
- Recruitment
  - [Recruitment of Women in the National Children's Study Initial Vanguard Study](#)
  - [Comparison of Recruitment Strategy Outcomes in the National Children's Study](#)
  - [The National Children's Study: Recruitment Outcomes Using an Enhanced Household-Based Approach](#)
  - [The Experience of the Direct Outreach Recruitment in the National Children's Study](#)
  - [The National Children's Study: Early Recruitment Outcomes Using the Direct Outreach Approach](#)
  - [The National Children's Study: Recruitment Outcomes Using the Provider-Based Recruitment Approach](#)
  - [Lessons from Prenatal Care Provider-Based Recruitment into the National Children's Study](#)
  - [Multilevel Provider Based Sampling for Recruitment of Pregnant Women and Mother-Newborn Dyads](#)
  - [Effectiveness of community outreach and engagement in recruitment success for a prebirth cohort](#)
  - [A review of social media methods and lessons learned from the National Children's Study](#)
  - [Leveraging social and digital media for participant recruitment: A review of methods from the Bayley Short Form Formative Study](#)
- Retention
  - [Participant Retention in a Longitudinal Study: Do Motivations and Experiences Matter?](#)
- Planned Missingness
  - [Improving cost-effectiveness of epidemiological studies via designed missingness strategies](#)
- Consent
  - [Consenting postpartum women for use of routinely collected biospecimens and/or future biospecimen collection](#)

## Memo on Study Design Considerations: Sampling and Power Analysis

Key points from a memo received from expert panelists:

- Starting suggestion for an optimal design
  - 20% opioid users.
  - 15-20% other substances (e.g., alcohol, cannabis, etc. can be polysubstance users).
  - 15-20% non-substance users with similar concurrent risk factors and life experiences (issues involving mental health, referral to CPS, elevated levels of adverse experiences, etc.).
  - 40-50% general population sample—Pregnant women who largely do not fall into any of the above categories.
  - To the greatest extent possible, the above distribution of study participants should be met within study sites.
- Sample size/power
  - Power calculation assuming a continuous outcome: you would have good power to detect effect sizes for main effects or interactions of .10 or larger with 2,000 opioid users and 2,000-3,000 comparisons, and even slightly better power if compared to general population sample.
  - As a starting place, the idea of a total cohort of approximately 8,000-10,000, oversampled to approach the sample characteristics described above may meet the study objectives as currently defined.