National Institute on Drug Abuse

HEALthy Brain and Child Development Study

Fall PI Meeting

November 16–17, 2020

Day 1 Videocast: https://videocast.nih.gov/watch=38117

Day 2 Videocast: https://videocast.nih.gov/watch=38119

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All referenced research is cited in the meeting recording and presenter slides—for further information about any research/report/article please review the recording.

Meeting Summary – Day 1

Welcoming Remarks (00:00:06)

Michelle Freund, Ph.D., Director, HBCD Study, National Institute on Drug Abuse (NIDA)
Nora D. Volkow, M.D., Director, NIDA
George Koob, Ph.D., Director, National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Dr. Freund welcomed meeting participants and indicated the goal of the two-day Fall Principal Investigator (PI) meeting is to learn about the progress made by each HEALthy Brain and Child Development (HBCD) Study-Phase I grantee/consortium despite the challenging conditions during the COVID-19 pandemic.

Dr. Volkow thanked Dr. Freund for leading the organization of this meeting and Drs. Gordon and Koob for their leadership and input. Dr. Volkow emphasized the relevance of the HBCD study, which became more urgent due to the opioid crisis and the need to understand how opioid exposure, alone and in combination with other drugs, during fetal development influences the brain. It is also important to determine how adverse environments prompted by drug use and exacerbated by the COVID-19 pandemic may affect infant development. The interaction of drug use with COVID-19 infection of pregnant mothers and its effect on child brain development must be studied. The Adolescent Brain Cognitive Development[SM] Study (ABCD Study[®]) has provided valuable information for adolescent development and early findings indicate it is also crucial to understand how the human brain works in early infancy through adolescence. The strategy of the HBCD Study investigators is to seek information to address the multiple insults affecting children.

Dr. Koob indicated the HBCD Study is particularly important due to the rise in alcohol consumption and other stressors caused by the COVID-19 pandemic. In the pre-pandemic era, about 10 percent of pregnant women reported alcohol use and almost 5 percent reported binge drinking. Alcohol use is highest in the first trimester of pregnancy. Abnormal facial features due to fetal alcohol spectrum disorders arise during the first trimester, whereas growth and cognitive issues can arise with alcohol use at any time during pregnancy. About 40 percent of women who reported using alcohol also reported using other drugs.

In the pandemic era, there has been an increase in alcohol use, which may be a response to stressors such as social isolation. Alarmingly, alcohol use is higher among women and women with children. Dr. Koob thanked the investigators and encouraged them to persist through the challenges of this pandemic.

Racial equity in Neurodevelopmental Research (00:07:45)

Natalie Slopen, Sc.D., University of Maryland

The life course perspective is a theory that unites both health equity work and neuroscience research, which are two fields that acknowledge health and health equity are shaped by the combination and accumulation of both protective and risk factors across the life course.

There are large and persistent racial and ethnic disparities in child health. A study of all preterm singleton births in the United States in 2017 found Black or African American, American Indian/Alaskan Native, and Hispanic mothers had increased risk of preterm birth compared with Asian/Pacific Islander and white mothers. Black and Hispanic children had higher rates of obesity and extreme obesity compared with white and Asian children (2011-2014), indicating these disparities begin early in life.

Comparison of suicide incidence rates between Black and white youths in the United States from 2001 to 2015 showed suicide rates were higher for Black children under 12 years of age, which contradicts the perception that suicide rates are lower among Blacks individuals relative to whites. These disparities are also evident in infection rates; Hispanics account for 45 percent and Blacks account for 29 percent of COVID-19-associated deaths among persons < 21 years in the United States.

Inequities in family socioeconomic status (SES) partially explain these disparities. One study found Black and Hispanic household income is lower than that of Asian or white American households. Another study showed the poverty rates among Black and Hispanic Americans were more than double those of white Americans in 2017. Wealth, an often overlooked factor of SES, has vast implications on child development, particularly during the COVID-19 pandemic. A study found white families held 10 and 8 times more wealth than Black and Hispanic families in 2016, respectively. As a result of these disparities, the financial challenges encountered by families during the COVID-19 pandemic are patterned by race. For example, a poll found a higher percentage of Black and Hispanic families, relative to white families, reported missed/delayed payment of major bills to ensure household members had enough to eat. Food insecurity, a well-documented social determinant of child mental health, is on the rise.

Disparities in child health by race and ethnicity persist across all SES levels. For example, one study found Black women had the highest infant mortality per 1,000 live births in 2016 at every level of education (e.g., high school, college degree). Studies found these disparities persist at every level of income for cases of child asthma and for COVID-19 mortality across neighborhood SES.

Child health disparities cannot be attributed solely to social class inequities; additional factors, such as individual and institutional forms of racism, are central to understanding disparities. Racism is a key determinant of disparate health outcomes and can impact child health. Neighborhoods, schools, medical care, and parent/caregiver experiences of discrimination are important social and contextual factors to child development and differ by race and ethnicity with implications for neurodevelopmental outcomes.

Racial residential segregation, a fundamental cause of health disparities, can lead to different opportunities and resources for healthy development for families of young children. One study ranking neighborhoods based on multiple dimension of opportunities (e.g., healthy food) found 70 percent of Black and 60 percent of Hispanic children lived in low or very low opportunity communities. These racial and ethnic inequities in neighborhood opportunity are also present for children living in poverty. Newly released data from the ABCD Study has allowed studies to connect neighborhood context to brain structure and function.

Segregation in schools, which is worsening, results in unequal education. According to U.S. Department of Education expenditure data, schools with 90 percent non-white students of color spend less per student than schools with 90 percent white students. One study found racial disparities in quality in New York City's universal pre-K program. Another study found that childhood educators tended to observe Black children more closely for bad behavior, resulting in implicit racism. Dr. Slopen noted treatment of children can have lasting impacts on their development.

Implicit biases must be considered because many studies within the HBCD Study may rely on observer reports and have implications for inequities within the healthcare setting. For example, one study showed Black children reporting moderate pain were less than half as likely to receive opioid analgesia relative to white children. Another study demonstrated that resident physicians in a pediatric emergency department had implicit racial bias against Black children similar to bias against Black adults.

Studies have identified factors such as parents' mental health that mediate significant associations of parents' experiences of racism with child health outcomes (e.g., cognitive development, healthcare utilization). Dr. Slopen highlighted the relevance of parent and family well-being for the HBCD Study and noted a family's social environment is important in understanding associations between brain structure and functional and behavioral

measures. The role of the environment and the importance of carefully measuring the environment and all potential confounders (e.g., parent education) in population neuroscience research must be recognized.

Inclusion of underrepresented populations in neuroscience research, with careful assessment of the social environment, is essential and has benefits for both neuroscientists and population health scientists, including greater generalizability of brain processes and mechanisms underlying behavior; enhanced knowledge about individual differences and diverse social experiences; improved understanding of how social context impacts biological processes; and broader possibilities for population-level impact of research findings. It is critical that neuroscience research reflects the racial profile of the United States population and it is advantageous to include representative as well as nonrepresentative, well-defined samples.

The inclusion of underrepresented minority participants in neuroscience research is particularly important in the COVID-19 era. Centers for Disease Control and Prevention (CDC) data show underrepresented populations have a higher rate of contracting the virus, hospitalizations, and deaths. Children of color are more likely to have parents who suffer severe COVID-19 consequences, which may have profound effects on their lives.

Attention to positive and protective factors to understand both between- and within-group differences is important and can inform efforts to address health disparities that begin early in life and emerge over time. One study showed inclusion of positive factors attenuated previously observed racial disparity of cognitive performance. Resilience-promoting factors for children of color exist at multiple levels and reliance-promoting policies have implications for child health and health disparities.

Discussion
Discussant: Nancy Jones, Ph.D., M.A., National Institute on Minority Health and Health Disparities (NIMHD)

Dr. Jones noted race and ethnic categories are sociopolitical constructs and reemphasized the need for a shift from considering race a risk factor to understanding the impact of racism and lived experience on different populations. The variables being measured require careful consideration—frequently, the social context and implications of belonging to a particular population are measured. In addition, examination of sampling and comparisons must be done; white individuals are often recruited from different locations and socioeconomic strata whereas minority population recruiting is limited.

Most biomedical scientists, including neuroscientists, do not account for community, population, or societal levels. Social scientists do recognize that population-level health disparities result from socially structured, quantitatively and qualitatively different, life experiences, stressors, and access to coping. Inclusion of measures of experience of racism, recognition of the lenses through which conclusions are made, and understanding of the direct and indirect effects of racism and how it alters health trajectories are important. Dr. Jones indicated scientific grounding imposes biases that affect how findings are made and reported. Thus, the fields of neuroscience and social science must come together. Promotion of diverse teams and creation of opportunities for neuroscientists and social scientists to jointly analyze and interpret data are needed. Community engagement methods are also important for understanding data.

The cultural competence of research teams, including those in the HBCD Study, has an impact on the research that is conducted. Thus, the lack of diversity in research teams must be addressed.

Determination of the best metrics to apply in studies such as the HBCD and ABCD Studies will ensure that data will allow researchers to ask the right questions and make correct conclusions. The HBCD Study offers the ability to follow children through their life course and an opportunity to separate the effects of race, SES, and neighborhood characteristics and their interaction. The spectrum of individuals (e.g., ethnicities) to include in studies must be defined.

There was discussion about the different tools used to measure experiences of discrimination and implicit bias. Currently, there are multiple broad and tailored tools for the assessment of individual or interpersonal

experiences of discrimination and implicit bias. However, these tools have limitations that must be considered. Dr. Pat Levitt suggested that the HBCD Study add a working group with expertise in population neuroscience to help structure studies.

Resilience-promoting factors are not intrinsic individual traits. Society can be structured so that resilience-promoting contexts are created to shape these factors and support individuals undergoing hardships.

Dr. Slopen indicated that studies have shown that obesity in young children is increased due to an imbalance of calories. Disparities in childhood obesity begin at an early age, and weight tracks over the life course.

Grantee Presentations (01:13:12)

Florida-Development in Early Childhood: Adversity and Drug Exposure (FL-DECADE) Study
Matthew Gurka, Ph.D.; Lisa Scott, Ph.D.; Kelly Gurka, Ph.D., University of Florida (UF)

Dr. Matthew Gurka presented an overview of progress on aims of the FL-DECADE study and future plans. Planning for Phase II is under way.

Aim 1 is to develop a comprehensive understanding of legal, ethical, and pragmatic factors that may impact effective recruitment and retention of high-risk participants in longitudinal research. This aim is being accomplished by holding a statewide summit that builds on a series of UF-led summits on early childhood and conducting a focus group study of pregnant women and mothers.

The statewide FL-DECADE summit titled Legal, Ethical and Pragmatic Considerations for a Prospective Cohort: Minimizing Risk and Maximizing Benefit was held virtually in May with over 150 participants, including representatives from state agencies, drug court judges, treatment/support program leaders, researchers, legal experts, providers, and women. Foster mothers and women with experience with substance use (SU) shared their personal experiences. There was a presentation on legal and ethical considerations and a discussion of relevant state programs. Breakout groups focused on mitigating risk and providing benefits, understanding changing family dynamics, and discussion of bias and stigma. The breakout discussions centered on brainstorming areas of future research.

Qualitative data from the breakout groups are being analyzed. During this summit, various connections were established with the Department of Health and the Florida Association of Healthy Start Coalition (FAHSC).

Dr. Kelly Gurka gave an update on the focus groups. To date, ten focus groups have been conducted. Two groups were recruited from an inpatient treatment program in Gainesville and eight groups were recruited virtually. Of the 33 women, 24 women were non-Hispanic white, 3 were non-Hispanic Black, 3 were Hispanic, and 3 were another ethnicity. About two thirds of the group lived in low-income households, a third had completed less than a college degree, two thirds were married, and three women were currently pregnant. Some women had newborns. The team found that a large number of women reported use of multiple drugs during pregnancy, including narcotic pain killers, marijuana, and sedatives, among others.

The team is conducting targeted recruitment of high-risk women in collaboration with the Healthy Start North Central Florida coalition, the Jasmine Project, and Families First. High-risk women who are not using substances are also being recruited. Additional focus groups with inpatient intensive program participants will be conducted virtually.

Aim 2 is to evaluate the feasibility of a multifaceted strategy for recruitment of a representative sample of pregnant women as well as an oversample of pregnant women using opioids or opioid treatment medications. Magnetic resonance imaging (MRI) protocols for Phase II are being established with the UF McKnight Brain Institute (an ABCD site). The team will begin recruitment of pregnant women using substances for a pilot study that will obtain clinical MRI scans on newborns. The LENA (Language ENvironment Analysis) device will be used to

record home language environment at four months. Cortisol of women and infants will be measured and electroencephalogram (EEG) will be done at six months of age.

Dr. Scott has designed a three-part EEG task to record EEG, event-related potentials (ERPs), and steady state visually evoked potentials (ssVEPs) in a longitudinal cohort of 6-, 9-, and 12-month old infants, allowing the team to determine the most robust measures. Due to COVID-19, infants have not been scanned since March. However, the team is developing publicly available EEG data processing pipelines and incorporating other publicly available pipelines into the data processing strategy in collaboration with Phase II co-investigator Dr. Andreas Keil. Dr. Scott has published data processing pipelines that may serve as a guide for processing infant EEG data and hopes these pipelines can become publicly available.

Institutional Review Board (IRB) approval was obtained for a Phase I pilot study to collect MRI images (e.g., resting state) of newborns. Scanning of infants for the Phase II application in collaboration with the McKnight Brain Institute will begin soon. The team is developing recruitment plans to allow for stratified recruitment of high- vs. low-risk families using the universal Healthy Start prenatal risk screen.

The Phase II recruitment strategy involves working with UF Health Clinics (e.g., UF Health Jacksonville) to expand recruitment to surrounding areas south of Gainesville, Florida and obtain a diverse sample of women. A collaboration with Healthy Start North Central Florida has been established to recruit high- and low-risk families that may or may not use substances.

Discussion

Women in focus groups were asked whether they were willing to be involved in a study like the Phase II study and in all aspects of the study (e.g., Would the women allow their children to participate in MRI study?). Differences in responses were observed between women who used substances and those who did not. For example, women who did not use substances were more reticent about participating in MRI studies.

Dr. Scott noted there is no portable EEG equipment available for image collection during home visits.

The Healthy Start screen is not home-visit-dependent and is administered by obstetricians during the first visit. There is variability in the individuals who are screened (i.e., screening depends on the provider's perception). An additional screen is done during a pediatric visit.

Salivary cortisol collection was done to establish feasibility of remote biospecimen collection for the pilot study during the COVID-19 pandemic.

There were IRB issues concerning recruitment of pregnant women who use drugs due to the use of the LENA device.

HEALthy ORCHARD
Daniele Fallin, Ph.D., Johns Hopkins University

Dr. Fallin presented progress of HEALthy ORCHARD working groups and subgroups. The Recruitment and Retention Working Group is divided into three subgroups: Qualitative Pilot Work, Ethical and Legal, and Methods and Considerations.

Recruitment for ORCHARD shifted to COVID-based recruitment targeting high risk for SU women in the first and second trimester of pregnancy through different partnerships (e.g., Johns Hopkins Center for Addiction and Pregnancy, and Women, Infants, and Children programs [WIC]). Focus groups consist of three different groups—WIC, Johns Hopkins, B'more for Healthy Babies—and are held virtually. Key stakeholder virtual interviews are conducted with service providers (e.g., social workers) in key organizations, family members, and focus group participants who prefer one-one-one interviews.

The Ethical and Legal subgroup aims to identify and develop strategies to address ethical challenges associated with recruitment, retention, data collection, and dissemination. The team is conducting an ethics evaluation to investigate the nature of the vulnerability of pregnant women who use substances and to provide a framework to determine whether the prospective benefits of the study could justify both the empirical and normative risks.

The Methods and Considerations subgroup is anticipating HBCD Study Phase II questions: What are the typical or normative neurodevelopmental trajectories for children from birth through childhood? And what are the effects of prenatal SU and other adverse exposures on development? The team generated recommendations to attain both external (generalizability) and internal (causal inference) validity, including prioritizing recruiting samples of women at high risk for SU to ensure prevalent SU exposures and to have overlapping key confounders to perform responsible association testing. Generalizability can be attained by collecting key characteristics on the sample, source, and target populations.

The Non-Imaging Assessment Working Group focuses on creating a set of working principles around data collection and a list of constructs to be captured. Annotation of these constructs for scientific rationale, feasibility, and acceptability is used to make final recommendations of essential and preferred items. Constructs relevant to brain imaging and co-occurring psychiatric and mental health conditions are selected. For example, prenatal SU exposure and prenatal stress is a family and environment key domain of interest.

The Neuroimaging Working Group is working with other imaging groups to develop an imaging acquisition protocol that can be used for infants and children across scanning platforms to reduce scanning time and ensure data harmonization. Scanning was delayed due to COVID-19 but will begin in December to assess quality, test the accelerated protocol, and demonstrate capability for young children.

The Biosampling Working Group focuses on generating a list of possible biosamples by timing window that are annotated by scientific rationale, feasibility, and acceptability to make suggestions of essential and preferred biosamples. The team is currently determining how to conduct neuroimaging, other assessments, and biospecimen collection.

The work of the Neuroimaging and the Qualitative Pilot Working Groups was most impacted by the COVID-19 pandemic. However, co-investigators deployed COVID-related studies in a Florida pregnancy cohort, including a Coronavirus Impact Scale and a new measure to assess the impact of mother and family member negative experiences with police on pregnancy outcomes. Another COVID-related study is examining the impact of COVID-19 exposure on maternal and neonatal outcomes.

For Phase II of the HBCD Study, the COVID-19 health consequences and social context (i.e., food insecurity, economic hardship, traumatic grief) as well as the non-COVID social context (i.e., heightened awareness of racial disparities and social justice and chronic trauma) should be considered.

Discussion

The team has prioritized exam room time to complete the scanning of children 6 months to 10 years of age that was delayed due to COVID-19.

The questionnaire assessing the impact of negative experiences with police is not being tested on Phase I participants. Police interaction questions will be shared.

COVID-19 research was funded through different supplements.

The Brain Begins Before Birth (B4) Midwest Consortium

Cynthia Rogers, M.D.; Christopher Smyser, M.D., Washington University in St. Louis School of Medicine (WUSM); Seema Shah, J.D.; Lauren Wakschlag, Ph.D.; Elizabeth Norton, Ph.D., Northwestern University (NU)

Dr. Shah presented progress on the legal/ethical aim. Data are being collected through a survey of obstetric providers to determine how punitive and nonpunitive laws regarding SU and pregnancy affect care provided and willingness to refer patients to research. The effects of bias and restrictive laws are tested using a hypothetical vignette. Qualitative interviews of pregnant women and community stakeholders/researchers studying SU in pregnancy are being conducted to identify barriers to recruitment and best practices.

Three themes have emerged from qualitative researcher interviews to date: usefulness of certificates of confidentiality (CoCs), importance of early stakeholder engagement, and significance of providing support/ancillary care to participants. Based on these themes, the team generated a list of preliminary best practice recommendations. CoCs are useful to engage participants and to create Memoranda of Understanding with local authorities; however, education on CoCs is needed. Early engagement with a broad range of stakeholders (e.g., SU treatment facilities) is critical. Building in referrals for participants' needs and ancillary care may help meet ethical obligations and ensure research success.

Dr. Norton discussed progress on the assessment and imaging aim and best practices for maximizing neurodevelopmental sensitivity with EEG. The team is comparing toddler EEG—including opioid-exposed toddlers—collected in the field with EEG collected in the lab to assess data quality and feasibility. EEG offers many advantages, (e.g., low cost) and outcomes are linked to neurodevelopment.

Lab-based EEG data collection from parents and children is ongoing at NU (24- to 26-month-olds) and WUSM (12- to 24-month-olds) using a BioSemi system that has a setup time of 30 minutes. Field EEG data are being collected using a portable Enobio system that has multiple advantages such as a short setup time. The team is recruiting 20 toddler-mother dyads to collect field and lab EEG data and compare those data with age- and SES-matched children from the existing study cohort.

The data harmonization goal is to use data science methods to harmonize B4 Consortium cohort data and determine how methodologic differences and exposure impact prediction by examining how varied characteristics of prenatal tobacco exposure influenced the prediction of birth weight from exposure-related risk. The team found nuanced characterization of prenatal exposure based on patterns of maternal behavior (i.e., quitters, intermittent smokers, persistent smokers) rather than dichotomous indicators (i.e., all smokers, nonsmokers) of fetal exposure alone can enhance the precision of exposure-related risk estimation. Cross-cohort data harmonization provides adequate statistical power to examine more refined exposure categories. This model will be applied to prediction of internalizing and externalizing problems using the same harmonized cohort, and the results will guide recommendation of optimal methods for drug exposure characterization in the HBCD Study.

Dr. Rogers summarized progress at WUSM, which includes recruitment of 15 opioid-using mothers from their opioid use disorder clinic and online clinical registries; establishment of a process with social services to retain foster care infants; ongoing multimodality MRI scanning of infants (including those exposed to opiates); and analysis of clinical MRI data from 34 neonates diagnosed with neonatal abstinence syndrome (NAS). COVID questionnaire completion by mothers across studies is ongoing.

The team is testing different retention strategies, including the mobile application uMAT-R, which was modified to contain study-specific modules, to investigate what material can be successfully deployed and whether app usage results in increased retention and staff time savings.

Discussion

Dr. Shah noted that laws in nonpunitive states give pregnant individuals priority access to treatment programs whereas punitive states consider SU during pregnancy child abuse or grounds for civil commitment. The team is investigating researchers' perceptions of the laws.

The case worker is the legal guardian and provides permission for the participant to continue to be part of the study. For these participants, the mother had consented to participation in the study before placement of the child in foster care.

Promoting Resilience in Children: Protocol Development for a Birth Cohort Study to Access Factors Impacting Neurodevelopment
Andrew Alexander, Ph.D.; Pilar Ossorio, Ph.D., J.D.; Ellen Goldstein, Ph.D.; Aleksandra Zgierska, M.D., Ph.D., Douglas Dean, Ph.D., University of Wisconsin (UW)

Dr. Goldstein presented progress on Project Aim 1: Develop protocols to engage and retain women with lived experience of SU while pregnant. The team has summarized and synthesized existing knowledge relevant to HBCD Study recruitment and retention by performing a literature review, surveying experts, and engaging diverse stakeholders. Qualitative in-depth interviews and focus groups with the target population have been completed. The team is currently testing selected recruitment strategies involving peer support. These activities will inform all three linked projects and Phases I and II of the HBCD Study.

A literature review was conducted on facilitators and barriers to recruitment and retention of pregnant women in prospective cohort studies with 500 most-recent publications and is under review.

A survey of experts to investigate their experience of supporting engagement of women from underserved and drug-using groups primarily addressed retention strategies—unlike the literature review, which focused mainly on recruitment.

A Stakeholder Advisory Committee (SAC) of diverse local stakeholders was established to better understand effective recruiting and retaining of pregnant women who use substances and participated in brainstorming sessions to identify barriers to engaging substance-using women in long-term research.

The team recently launched a pilot study of peer-support-assisted research engagement strategies to study the impact of peer support on recruiting and retention. The participants—women with lived experience of SU during pregnancy or early motherhood—will be randomly assigned to a certified Peer Support Specialist who has received pregnancy training or a research coordinator. Outcome measures include recruitment and follow-up visits. Participants' experiences with and without a peer navigator will be assessed to help understand barriers and facilitators to future birth cohort studies.

Dr. Dean summarized progress on Project Aim 3: Development and evaluation of protocols for pediatric neuroimaging and neurocognitive assessment to inform the HBCD Study Phase II. COVID-19 human subject research protocols have been established and recruitment has resumed—5 children (0–10 years of age) have been recruited to date and 34 children (0- to 2-year-olds) have been recruited for a separate study. In total, 17 individuals have been scanned during sleep (with acoustic noise reduction for children <4 years old) and awake (children >4 years old) periods.

The team has developed a protocol to obtain robust structural images using MPnRAGE, a technique that results in quieter imaging by implementing retrospective motion correction. The team is also using DESPOT/mcDESPOT, which allows for high-resolution T1 and T2 relaxometry maps and capture of lower resolution images for myelin water fraction imaging. A functional near-infrared spectroscopy (fNIRS) protocol and modified Stroop task geared towards children >4 years old have been developed with great success.

Dr. Ossorio discussed progress on Project Aim 2. To date, legal analysis has been completed for 36 states. The 50-state legal analysis will be completed by the end of the year and detailed results will be shared through a web platform. The law pertaining to prenatal substance exposure varies depending on whether a pregnant woman or a newborn is considered; in different states, prenatal drug exposure is determined by positive toxicology report or a diagnosis of newborns. The greatest legal risk to participants is a newborn's positive toxicology report. More than 50 percent of states legally require that positive toxicology be reported to child abuse investigating authorities. This information will impact memoranda of understanding (MOUs). Diagnosis of a newborn or young child as substance-affected carries intermediate risk, whereas the lowest legal risk to participants in most states is evidence of a woman's use of controlled substances during pregnancy and before a baby is born.

Prior to 2016, CoCs did not prevent investigators from deciding whether or not to disclose sensitive information. However, current CoCs explicitly forbid disclosure of information unless required by law or the participant gives permission. It is important that institutions display the correct information regarding CoCs. Education around CoCs is necessary. Dr. Ossorio indicated that in many states, the legal risks will be greatly reduced if researchers do not also provide healthcare or social work services to research participants. There are great implications for recruitment and service referrals.

Recruitment and Retention (03:02:49)
Study Design Working Group: Recruitment and Retention Considerations
Aleksandra Zgierska, M.D., Ph.D., Pennsylvania State University; Florence Hilliard, M.S., UW

Dr. Zgierska presented work done by the Recruitment and Retention subgroup of the Study Design Working Group. Reduction of fear, provision of an enjoyable experience, and building of relationships and trust are critical to recruitment and retention. Population data, such as Big Data, are helpful in guiding recruitment and retention strategies; however, they may lead to bias. Preliminary analysis of state-level data revealed clinical recruitment is feasible but may be biased.

A broad literature review identified general recommendations for recruitment, including leveraging existing relationships, creating opportunities for social support and networking among participants (i.e., mothers, guardians, children), and employing well-trained, dedicated recruiters who present the study in an understandable manner and demonstrate genuine concern for participants' well-being—using clinicians as recruiters may pose a barrier to recruitment. In addition, existing frameworks (i.e., marketing) must be applied to help researchers develop and test recruitment and retention strategies and timelines.

The DEEP research implications for research are:

- <u>D</u>evelop theory-driven and evidence-based recruitment strategies during the planning phase.

- <u>E</u>ngage appropriate stakeholders during all phases of research, including planning.

- Develop <u>E</u>ntrusted relationships with well-trained, trust-building, and dedicated staff.

- <u>P</u>lan for multiple recruitment strategies such as nonmonetary incentives that are appealing to participants (in addition to traditional reimbursement).

Recommendations for retention include consistent, culturally sensitive communication from respectful, knowledgeable study staff; use of multilayered retention strategies; and employment of staff who share background traits (e.g., race) with participants. Investigators must plan for retention of participants and provide staff training, and employ staff with the necessary soft skills. The participants' burden must be reduced by maintaining flexibility in the retention plan and including psychosocial and/or material support. Thus, researchers must focus on participants, employ staff who are solely dedicated to retention, and budget for retention.

A second literature review focused on pregnant women engaged in prospective studies and revealed that recruitment and facilitators are more thoroughly described than are retention and barriers. Technology (e.g., social media) is very useful; however, investigators must also use traditional communication tools. There is an emphasis on the use of technology for recruitment, not retention. Social media have ethical and legal aspects and a potential for bias. Technology is critical for studies (e.g., e-consent).

The responses from a survey of 70 experts across HBCD Study groups on advice for engagement of pregnant and postpartum women with addiction in long-term studies focused on retention rather than recruitment and corroborated the literature review findings. Preliminary analysis found that building relationships, accommodating participants' needs, and limiting participants' burden are key.

Dr. Hilliard discussed the perspectives of the SAC, which is composed of state departments and law enforcement representatives, legislators, treatment providers, local organizations, and women with lived experience of SU during pregnancy and/or motherhood. The main barriers and proposed solutions to engaging women in research identified by stakeholders in the first meetings were the following:

- Shame/fear of judgment—solution: build in ongoing feedback from the target population.

- Fear of legal consequences—solution: modify state and federal laws, and focus efforts on states without severe legal costs.

- Lack of trust in confidentiality—solution: recruit through trusted partners, provide peer support, and practice relationship building.

The team developed a 37-item Questionnaire Guide using stakeholder input to investigate both barriers and motivators for women to join and continue in the study. In total, ten in-depth interviews were conducted virtually, and seven women participated in two focus groups. For recruitment, having a trusted partner—a person they knew who was participating in the study or a trusted peer support specialist—was especially important. Other preferred trusted partners included women's SU treatment centers and their counselors, hospitals and clinics, primary care clinicians, community agencies, and culturally specific community centers. Women favored a warm and welcoming female recruiter with knowledge and experience with addiction. Social media (i.e., Facebook) were preferred methods of communication.

Word of mouth is important for recruitment in rural hospitals and clinics. There is mistrust of social workers and amongst healthcare professionals and women of color. Women responded that the most valued incentives for retention are multiple-use gift cards, baby supplies, peer support throughout the study, access to legal services and advice, and housing and childcare aid.

Study teams can implement effective recruitment and retention strategies in the current social and physical distancing climate by employing technology and user-friendly e-consent. Inclusion of historically underrepresented groups in research can be increased by budgetary investments, detailed planning of recruitment and retention strategies, involvement of peer support specialists, and cultural sensitivity and a patient-centered approach.

Peer support specialists are actively involved in research and require training in research and the targeted condition. Bidirectional training of both peers and researchers/staff is critical.

Discussion

There was discussion about different ways to provide legal support to participants. Biomedical research groups could partner with legal clinics. Legal advice could also be provided by the institution's legal clinic staffed by law students and overseen by practicing lawyers. The 50-state legal analysis will be a resource for legal clinics providing support to participants.

Co-Creation of Knowledge for Meaningful Recruitment and Retention in Research
Judy Illes, C.M., Ph.D., University of British Columbia (UBC)

Dr. Illes described lessons learned from a recruitment and retention strategy utilized in an Alzheimer's case study of a population in Northern Canada and a systematic review of studies involving Aboriginal children. In 1997, researchers discovered a Tahltan population in a remote part of British Columbia carried a presenilin 1 mutation putting them at risk for early-onset Alzheimer's disease. Joint research planning, knowledge sharing, and sharing of results proved critical in engagement of this population in research.

The planning phase of the study involved community-based research (CBR). Meetings were held with stakeholders (e.g., UBC principals, researchers, community elders) to understand the community's previous experience with research, frame research questions, ask questions relevant to the community, and outline future research. Community-based participatory research (CBPR) defines the roles and responsibilities for researchers, participants, and partners; clarifies the processes for collaboration to create research questions and ethics approaches; and emphasizes community action and capacity building as research outcomes.

Researchers learned about the traditional views of the Nation and its disconnection to biomedicine and found there were fractures in intergenerational knowledge. They also learned about the power of caring and the importance of territory and tradition. Joint understanding of the disease led to increased recruitment of participants and their families and acceptance of the research.

Results were shared through academic products and briefings. A book and a child's guide to Alzheimer's disease were also produced and distributed throughout the community. Feasts with the community served to share acquired research knowledge and results. The research question co-created with the community became: How does a Nation achieve wellness in early-onset familial Alzheimer's disease?

A systematic review of studies involving Aboriginal children published between 1981 and 2011 from Canadian universities revealed the majority were focused on fetal alcohol syndrome. Lessons learned about recruitment and retention will be used to understand fetal alcohol syndrome in these communities.

Dr. Illes discussed the main conclusions of the Alzheimer's study. Prestudy participatory consultation is essential. Regional guidance and regulation may vary, and western ethics may be irrelevant. Researchers must prepare for unexpected results and challenges (e.g., mental health challenges); understand that the concept of time differs among different stakeholders; and embrace the opportunity to co-create led by those they seek to serve.

Discussion
Discussant: Kathy Etz, Ph.D., NIDA

TCPS has been very helpful in guiding research in indigenous communities in the United States. Dr. Etz indicated the National Institutes of Health (NIH) is developing guidance for data policies focused on sharing and ownership of data, which will be useful for HBCD Study researchers. She encouraged HBCD Study investigators to consider the following lessons on community engagement strategies resulting from CBPR. Existing frameworks that can be useful in engaging participants include community health workers. Researchers should consider that technology is not available equally amongst communities. NIDA researchers conducting research with indigenous communities observe that face-to-face interaction with participants is necessary for engagement.

Dr. Hilliard clarified that for recruitment, women preferred a woman from their community that they trusted and was in recovery. Dr. Zgierska stated that finding researchers that belong to specific subgroups is costly and challenging; thus, researchers are employing stakeholders with established trust with participants. In addition, requesting feedback from stakeholders and gaining their trust takes time. Implementation of their feedback ensures that stakeholders become team members. Dr. Amy Elliot highlighted that engaging communities as true partners solidifies long-term relationships.

Defining where observational research ends and intervention begins is challenging. Considering the role of peer specialists may help in defining these roles. Peer specialists do not deliver services but are navigators that forge connections and maintain relationships, trust, and support.

There was discussion about the challenge of implementing CBPR as part of the HBCD Study, which will include participants from different tribal communities. CBPR may vary depending on community type (e.g., urban and non-tribally affiliated areas, tribal communities).

For Phase II of the HBCD Study, there is currently no established protocol to manage incidental findings. It is hoped that a protocol will be developed prior to the start of the study. To address incidental findings, establishment of a coordinating center to provide ethical and legal support for individual teams and community advisory boards was proposed. Dr. Terry Jernigan, lead of the ABCD Study Coordinating Center (CC), noted that with a large study, such as the HBCD Study, issues of incidental findings will be ongoing. She indicated that in the ABCD Study, a task force was formed with counsel from bioethics and medical oversight groups, the Observational Study Monitoring Board, and other consultants to develop a process to determine whether there should be returned results for specific incidental findings.

Grantee Presentations (04:45:44)

Motion-Resilient MRI in Early Childhood
Dylan Tisdall, Ph.D.; Allyson Mackey, Ph.D., University of Pennsylvania (UPenn)

Collection of measurements in preschool-age children using different methods (e.g., scanning) is difficult. Thus, the team has developed infant- and toddler-ready structural MRI methods, evaluated the feasibility of a movie-based functional MRI (fMRI) task, and developed new tools for repeated remote measurement of children's environments and behaviors.

Dr. Tisdall described progress on the development of infant- and toddler-ready structural MRI and sequence dissemination to study sites. The team has achieved integration with Framewise Integrated Real-Time MRI Monitoring (FIRMM) software to attain real-time display of subject motion; developed a vendor-agnostic real-time motion-tracking system; generated offline analysis and tuning tools; simplified the on-scanner workflow; and enabled pre- and post-readout navigator placement.

The team is collaborating with different sites to gain access to a pediatric cohort. Limited testing and validation in adults is ongoing at UPenn. This sequence will be an added feature at five sites acquiring infant and toddler scans, and the data will be shipped to the team for evaluation of the infant/toddler motion-tracking algorithms. The modified sequences will be rapidly disseminated to test sites. Thus, rapid validation will be accomplished while data acquisition at UPenn is on hold due to COVID-19.

The team evaluated compressed sensing (CS), a structural scanning technique that accelerates scans, in preschool-aged children prior to the COVID-19 shutdown. CS scans are being collected by Dr. Hao Huang's ongoing study at CHOP. Joint vNav-CS sequences will be available on new Prisma software that will be released before Phase II.

Dr. Mackey discussed the movie-based fMRI task and repeated remote measurement of children's environments and behaviors. The team compared naturalistic movie viewing to rest to determine whether children move less when watching a movie with rich parent-child dynamics (Pixar's Piper) than when looking at a fixation cross and whether younger children benefit more from watching a movie. The team found children move less when watching a movie than in pure rest. Movie watching was particularly helpful for younger children (>7 years old).

The team predicted that children experiencing harsher parenting would be less reactive to specific events in the movie. Thus, child-parent interactions in the home were studied using new tools for repeated remote measurement of children's environments and behavior. With the goal of establishing reliable brain-behavior

relationships, the team determined daily fluctuations in children's persistence by asking parents of 3-year-olds to take videos of their children during nightly toothbrushing for two weeks (allowing coding of child and parent behavior). The parents were also asked to answer a daily questionnaire on parent stress, child mood, and child sleep. The team found that fluctuations in encouragement predicted fluctuations in brushing time, parents do not encourage less while more stressed, and children brush longer when in a good mood. However, some children are very sensitive to parents' stress and sleep. In addition, higher encouragement is associated with higher SES.

The IMPACT Study: Imaging Prenatal and Pediatric Populations to Ascertain Childhood Transitions and Tenacity in Children with Opioid Exposure
Ashley Acheson, Ph.D.; Xiawei Ou, Ph.D., Arkansas Children's Research Institute (ACRI) ; Weili Lin, Ph.D., University of North Carolina, Chapel Hill; Stephanie Merhar, M.S., M.S., Cincinnati Children's Hospital (CCH); Nancy McElwain, Ph.D., University of Illinois; Brian Smith, M.D., Duke University

Dr. Acheson presented an overview of the Consortium's organization and new fetal imaging and pediatric longitudinal protocols. Duke Clinical Research Institute (DCRI) is the coordinating center for four study evaluation sites. The University of North Carolina at Chapel Hill leads image and data analysis, the University of Illinois oversees the development of the LittleBeats (wearable) device, and ACRI leads the development of Virtual Home Observation for Measurement of the Environment (HOME).

The Consortium is collecting fetal MRI imaging data, including structural and diffusion-weighted imaging and motion tracking, from women who used opiates during pregnancy. Biospecimen collection and a psychiatric, cognitive, and environmental battery will be performed.

The team is using the LittleBeats device, a wearable mobile sensing device (records audio, motion, and electrocardiogram [ECG] signals) to capture 3D child motion, stress regulation, and parent-child interactions. A pilot study of LittleBeats (version 3) with 3- to 12-month-old infants was performed and the team concluded most data (91%) were good. LittleBeats ECG and wireless BIOPAC monitor ECG data were compatible. The team will track motion during parent-child interactions. LittleBeats motion tracking had better resolution than that of smartphones. Speech processing algorithms are being developed to classify speakers and vocalizations.

Virtual HOME is being used to assess parent-child interactions and home environments. Advantages of virtual administration of HOME include accessibility, cost reduction, decreased burden and staff safety risk, and adaptability to large-scale multisite studies. Virtual HOME may be optimal for the HBCD Study Phase II, although full assessment of the environment may require additional questions.

Dr. Smith summarized study coordination activities. ACRI coordinated multiple activities across sites (e.g., timeline management, single IRB study and site-level submissions, study document management, communications, database management, and statistical support).

Dr. Ou presented on analysis of existing MRI data from Phase I and other relevant projects. ACRI is conducting several studies to investigate how different maternal factors affect infant brain development. Investigators found pregnant women's fat mass percentage was negatively correlated with newborns' cortical thickness. Mental health of pregnant women negatively correlated with white matter development whereas pregnant women's physical activity positively correlated with white matter development. These results suggest that multiple covariates must be considered for Phase II. Comprehensive characterization of pregnancy is needed to delineate the effects of prenatal substance exposure.

Fetal (36 weeks' gestation) and postnatal (7 weeks old) imaging of subjects from Phase I showed fetal MRIs are feasible and valuable in characterizing early brain development; particularly, evolvement of cortical folding. Analysis of functional connectivity (fMRI) data collected from infants during sleep and wakefulness (watching a movie) revealed that lower functional connectivity occurred during sleep, indicating that scan mode is an important confounding factor that must be considered during analysis.

Collection and analysis of MRI data during Phase II may have additional challenges. There will be a need for real-time quality control and motion correction techniques to address artifacts; tailored image analysis tools for analysis of neonatal and pediatric images; and image harmonization. The Consortium has developed automated real-time quality control processes that work well across different platforms and deep learning approaches to salvage corrupted images. Effective harmonization tools have been developed to harmonize images as well as cortical thickness and surface area measurements collected with different protocols in different sites. The iBEAT 2.0 software facilitates consistent postprocessing (e.g., cortical surface reconstruction, tissue segmentation) of images across different scanners and will be available soon.

Investigation of Opioid Exposure and Neurodevelopment (iOPEN)
Damien Fair, Ph.D., Oregon Health & Science University (OHSU); Alexandra Potter, Ph.D., University of Vermont Medical Center; Moriah Thomason, Ph.D., New York University School of Medicine (NYUSM); Ashok Panigrahy, M.D.; Elizabeth Krans, M.D., M.Sc., University of Pittsburgh

Dr. Thomason outlined iOPEN goals achieved during Phase I, including developing a protocol leveraging multiple channels of recruitment to inform study design and establish relationships for Phase II; generating a protocol with cross-site training, coordination, longitudinal and multimodal assessment, and toddler MRI; assessing neuroimaging techniques to address current limitations and facilitate optimization; and focusing on building community partnerships and retention.

The team conducted a survey study across all sites with pregnant women and new mothers and their partners to evaluate effectiveness of recruitment methods (i.e., social media, clinics).

The team launched two protocols: longitudinal perinatal assessment (infant MRI) and toddler (age 3 years) MRI. Both protocols included mothers who used opioids during pregnancy. Due to COVID-19 restrictions, a remote recruitment and longitudinal assessment strategy involving prenatal recruitment and biobehavioral assessment of mothers and children (at 3 and 6 months of age) was implemented. Remote six-month assessment activities included an armrest paradigm, free play with and without toys, visual attention, and a still face paradigm. Lessons learned from this remote assessment include the need for flexibility (families have diverse needs that may change), strong documentation to maintain measurement validity, and active relationship building. The team developed the Covid-19 and Perinatal Experiences (COPE) study and established the COVID Generation (COVGEN) alliance.

The team found that active relationship building, ensuring of diversity in remote recruitment, and creation of processes for remote biospecimen (e.g., blood) collection were challenging and important for success of studies. Informational and explainer videos were created to increase study visibility and prepare participants for study activities such as biospecimen collection.

All study sites are assessing neuroimaging techniques across sites by conducting MRI imaging with COVID-19 precautions. MRI imaging innovations, such as volumetric navigators, 4 echo planar imaging (EPI), sensitivity encoding, 4-shell DTI, and FIRMM, are being implemented and tested. The group has successfully relied on the Open Science Framework (OSF). Participant preferences were determined by surveying a group of diverse pregnant women and new mothers. Participants preferred communication via text messages, small gift cards, and shorter surveys. Participants also preferred to be contacted frequently. There was a slight preference to receive surveys during the day.

Dr. Krans discussed lessons learned from conducting research with substance-using pregnant and parenting women and iOPEN stakeholder advisory committees to learn how to engage substance-using individuals in research because there is a need to support widespread acceptance of research participation by substance-using individuals.

Meetings with stakeholder advisory committees composed of providers, individuals and families with lived experience of SU, state health and child protection agency representatives, community organizations, and influencers were held across all sites. Substance-using persons were enthusiastic about contributing to future research but did not trust existing research or interpretation by medical providers and child welfare agents.

In longitudinal studies, the group learned how to improve the process by conducting qualitative interviews with the participants. Barriers to recruitment of substance-using individuals include limited healthcare utilization outside treatment settings (treatment facilities may not allow research recruitment), mistrust of the system and others (e.g., family, friends), competing demands (e.g., work schedules), and prohibitive study requirements (e.g., excessive paperwork). Recruitment facilitators include trust, enrollment from settings where participants receive clinical services, utilization of trusted providers, compensation, and staff interested in working with this population.

Barriers to retention include inability to complete in-person assessments, lack of consistent contact information and residence, and personal issues (e.g., child custody problems). Retention facilitators include conducting in-person assessments judiciously, using paid transportation services, and obtaining contact information from participants' family members/friends. Researchers must also use multiple ways to contact participants—almost all women use text messaging and many use email.

Discussion

Dr. Tisdall clarified that vendors would not get an exclusive license to vNavs—it can be used for research and across vendors.

Dr. Cathy Spong noted that the COVID-19 pandemic is impacting studies' findings. Thus, investigators must try to differentiate supplemental funding to study the impact of COVID-19.

For blood collection, participants receive two kits. The samples must be processed within 24 hours, which is a challenge due to the cost of shipping. Adaptation of the blood collection device for collection from children is being considered.

Participants briefly discussed the use of single IRBs. Dr. Thomason noted that the coordinating center will facilitate implementation of a single IRB. Dr. Jernigan noted that implementing a single IRB for a large study involving multiple sites is extremely important and relieves the burden on sites, although it does pose various challenges.

Dr. Lin indicated the team is focusing on harmonizing fMRI data collected from infants during sleep and wakefulness (watching a movie) to facilitate analysis in longitudinal studies.

Meeting Summary – Day 2

Grantee Presentations (00:00:03)

Cumulative Risk of Substance Exposure and Early Life Adversity on Child Health Development and Outcomes

Sean Deoni, Ph.D., Brown University; Amy Elliott, Ph.D., Avera Health; James Blair, Ph.D., Boys Town Research Hospital; Charles Nelson, Ph.D., Harvard University; Nathan Fox, Ph.D., University of Maryland

Dr. Fox presented current progress on the Consortium aims. Studies have been significantly affected by the COVID-19 pandemic, and some sites have been conducting recruitment remotely. Accomplishments across all sites include development of protocols for infant and toddler MRI, development of standardized EEG procedures, engagement with several working groups, and piloting of remote and virtual visits as well as recruitment procedures.

At the University of Maryland, 71 percent of women, including substance-using pregnant women, that were recruited remotely were retained. The group has completed a postnatal scan of a 6-week-old infant. Retention efforts include contactless delivery of diapers/blankets to participants and a COVID-19 MRI safety procedure video.

Boston Children's Hospital and other sites collaborated to generate standardized EEG preprocessing procedures. Nonlinear EEG measures have been established to assess predictability and complexity of the signal and help predict developmental outcomes.

At Boys Town National Research Hospital, the team has successfully recruited substance-using parenting women. Of these, 14 percent are substance-using women, 35 percent have mental health concerns, and 10 percent are below the poverty line. Infant scanning has resumed with COVID-19 precautions. The 3-month-old scanning protocol has proved effective.

The Virginia site has held discussions with the Central Appalachia HBCD Community Advisory Board (CAB) on navigating the legal and ethical complexities associated with coordination, communicating of services to study participants, updating recruitment/retention protocols, and identifying additional partners across Central Appalachia. Feasibility protocols have been updated in response to COVID-19.

Dr. Deoni described progress on MRI imaging optimization and development of mobile MRI. The team is working on reducing acquisition time of high- and low-resolution images and increasing processing speed to gain an understanding of brain development trajectories. Functional and connectivity imaging techniques and probabilistic independent component analysis are used to relate cognitive domains with development of specific brain regions (i.e., myelination). This correlation analysis is also applied to compare qualitative data with quantitative data from the cortex. The team found limited cortical associations (associations between rate of cortical change and rate of cognitive change) in children between 1 and 5 years of age. However, there were intra-cortical myelin associations. The team is determining how these associations evolve with age using functional correlation models that allow quantification of continuous relationships between brain structure and maturing cognitive function.

The team is also focused on devising ways to conduct remote data collection—a significant aim of the Consortium—to reach participants in distant rural communities. A single wearable device that collects various data (e.g., EEG) is being developed in collaboration with a Silicon Valley company. The Epilog system is another wearable device the team is testing to conduct at-home EEG data collection. This device is reusable, is chargeable, and has a battery life of 20 days. In collaboration with Sibel, the team is building reusable EEG arrays.

In addition, the team is using the novel, low-field, Hyperfine mobile MRI system to perform high-quality structural imaging in infants. This system has low cost and power requirements (i.e., 4-hour battery life), can be safely

transported in a modified van to different locations, and offers T1, T2, FLAIR, and diffusion-weighted imaging (DWI). Images collected with this system are comparable to those collected with an 8-channel 1.5T system. Dr. Deoni conducted the first live demonstration of the device at a participant's home. The group hopes to expand this effort globally, perform population studies, and apply other imaging techniques. The team carries an Epilog system with the mobile MRI system to collect EEG data.

Discussion

The Hyperfine MRI system is very resilient to motion. In addition, it does not require shielding, which enables scanning to be done in any setting. Imaging can be done with newborns, children, and adults. Images can be processed using various software applications, including FreeSurfer. The team is using artificial intelligence (AI) technology to conduct image quality transfer and integrate collected data with 3T data. DWI works well; however, the system cannot do echo-planar imaging or magnetic resonance spectroscopy. Additional approaches that could be used are longer diffusion gradients, steady-state based fMRI, and arterial spin labeling. The estimated cost for the full mobile system is about $100,000.

Planning for the HEALthy Early Development Study
Christina Chambers, Ph.D., M.P.H., University of California; Ludmila Bakhireva, M.D., Ph.D., M.P.H.; Julia Stephen, Ph.D., University of New Mexico (UNM); Claire Coles, Ph.D., Emory University; Julie Croff, Ph.D., Oklahoma State University (OSU); Lynn Singer, Ph.D., Case Western Reserve University

Dr. Chambers presented current accomplishments of the 5-State Alliance for HEALthy Early Development Research (5-STAR) Consortium. The team has contributed to multiple publications with topics such as lessons learned for the opioid epidemic and engaging pregnant and postpartum women at risk of substance abuse in longitudinal studies that will inform study design for Phase II. Additional Consortium publications focus on recruitment and retention, ethical issues and informed consent, biospecimen collection, neurodevelopment and contextual factors, and neuroimaging.

The Consortium began conducting focus groups to study perceptions of high- and low-risk women on recruitment and retention and inform Phase II. Lessons learned from analysis of this qualitative assessment include:

- Participants prefer recruitment at medical locations and childcare facilities and would feel most encouraged to join the study by trusted individuals (e.g., medical personnel).

- Enrollment decision making is facilitated by informing participants about the study, risks, benefits, and staff availability.

- Benefits of the study and compensation are motivators for recruitment whereas factors such as busy schedules, transportation, and childcare are barriers.

- General research support (e.g., childcare), flexibility (e.g., appointment scheduling), relationship with staff, and research updates are needed for retention.

- There are multiple family-related barriers to retention, including childcare, busy schedules, and loss of interest in the study.

- Identified barriers and facilitators did not differ substantially between the two groups. However, high-risk women consider compensation/incentives as very important for recruitment and retention.

The team is conducting a pilot study to collect infant respiration data remotely using novel crib sensors. Feasibility of overnight respiratory monitoring was established, and respiratory data can be viewed across multiple time scales. A pediatric sleep specialist reviews the data.

Working groups within the Consortium have been established. The Recruitment and Retention Working Group has generated a handbook of best practices for ethical recruitment and retention. Readiness of all five sites for the Phase II study has been evaluated. Recruitment sites have indicated the ability to recruit high- and low-risk women. Capacity to conduct neuroimaging, maternal/infant assessment capacity, and strategies to address legal/ethical barriers to recruitment/retention have been assessed. Groups have received a number of COVID-19 HBCD Study R34 and non-HBCD Study supplements to evaluate effects on different cohorts of pregnant women, infants, and mothers caring for children.

Dr. Stephen presented findings from a study that integrated structure and function to understand neurodevelopment. The team examined altered brain function in preterm and term infants by conducting magnetoencephalography (MEG)—with an auditory oddball task (AOD)—and MRI imaging in 18-month-old infants. There was positive correlation between the amplitude of AOD response and anterior cingulate volume in term infants but not in preterm infants, suggesting that the anterior cingulate is relevant to the AOD response, as observed in studies with adults. These data motivate the multimodal approach to provide insight into how structure influences function in children.

Dr. Chambers outlined considerations in substance exposure measurement. For prenatal substance exposure assessment, an accurate evaluation of quantity, frequency, and gestational timing is needed. Most drugs have small to medium effect sizes on neurodevelopmental outcomes. In addition, threshold effects can be missed with dichotomous classification, and averaging quantity and frequency may yield underestimates of exposure. First-trimester effects of substance exposure must be considered. Currently, there are no birth biomarkers that assess first-trimester exposure. Pregnant women tend to decrease drug use over the course of pregnancy. Averaging quantity over pregnancy or using biomarkers that can only measure second- and third-trimester exposure may miss effects; thus, self-report is needed to assess the full range of exposure. However, factors such as stigmatization and risk of incarceration hinder prenatal exposure assessment. Confounding factors include polydrug exposure, prenatal family environment, and postnatal factors (e.g., family environment, medical fragility).

Dr. Bakhireva discussed essential, alternative, and recommended data elements for prenatal targeted analysis. The use of biomarkers yields information that is useful to address potential underreporting of substance exposure. The Biospecimens Working Group generated a list of essential and recommended biomarkers for different domains. Essential biomarkers for the SU exposure domain for mothers include prebirth urine and nail clippings (alternative: hair) and urine at time of delivery. Essential biomarkers for children include urine (alternative: saliva) and cord tissue (alternative: meconium) at delivery and urine (alternative: saliva) for the first two years.

To evaluate medical fragility as a confounding factor and understand its effect on retention, postdischarge healthcare utilization in infants with neonatal opioid withdrawal syndrome (NOWS) identified in the CERNER Health Facts® database was analyzed. Compared with uncomplicated births, NOWS children had increased risk of hospitalizations during the 1 year and 30 days period after delivery. NOWS severity was associated with an increased risk of unplanned healthcare utilization. Potential implications for the HBCD Study include considering pharmacologic and nonpharmacologic treatments and hospitalizations/emergency room visits as important confounders, and recognizing that the medical fragility of NOWS children may have implications (e.g., retention).

Recommendations for assessment include combining self-report data and biomarkers to quantify prenatal exposure; assessing confounders pre- and postnatally; ensuring nonjudgmental, private, confidential, and culturally sensitive interviews, compensating for time and effort; identifying needed resources for families; and separating research from mandate to report.

Respiratory rate and sleep, which are continuous and noninvasive markers, will be studied in prenatal substance-exposed and non-substance-exposed infants to determine effects on sleep and respiration development. In future studies, sensors could be combined to collect different measures simultaneously.

The 5-STAR Consortium sites have identified MRI scanning locations that will not be prohibitive to participants.

Planning Phase for the HEALthy Brain and Child Development Study (HEALthy BCD) in Los Angeles County Area
Wei Gao, Ph.D., Cedars Sinai Medical Center

Dr. Gao described progress on aims, including team building, recruitment and retention, imaging, and data analysis. The team is highly interdisciplinary and is composed of obstetricians/gynecologists, pediatricians, developmental psychologists specializing in infant cognitive assessment and EEG, imagers, statisticians, a substance use disorder (SUD) clinical research partner, and consultants.

In the pre-COVID-19 pandemic era, two focus groups with 12 women total were conducted. Dr. Gao discussed retention of patients from either Cedars Sinai Medical Center or Tarzana Treatment Center (TTC). The study design included four groups: mothers using opioids alone or with other drugs (POE), mothers using drugs other than opioids (PDE), matched drug-free high-risk controls who have other risk factors (MCTL), and representative individuals (RS) who may overlap with the other groups. Out of 8 pregnant women recruited from TTC, 4 remain active, all completed the three-month assessment, and 2 completed the six-month assessment. Contact with four women has been lost due to multiple reasons (e.g., premature delivery, premature exit from treatment facility).

On the other hand, retention of women recruited from Cedars Sinai has been effective. All 13 representative women recruited from Cedars Sinai are active, 3 have completed neonatal visits and MRI imaging (halted due to COVID-19), all have completed the three-month assessment, and 11 have completed the six-month assessment.

During the COVID-19 pandemic, the team has focused on recruitment and retention of women in the RS and MCTL groups. From Cedars Sinai, 102 women from a high-SES area were recruited through multiple channels (e.g., obstetrical clinics, in-person, mail). From Harbor-UCLA, 25 women were recruited from a low-SES area through obstetrical clinics.

Drug exposure data of the groups recruited through TTC, Harbor-UCLA, and Cedars Sinai Medical Center show that of the women recruited from TTC, half were in the POE group and half were in the PDE group. The opioids used included heroin, morphine, methadone, suboxone, and marijuana. Women in the PDE group used three of four drugs (i.e., marijuana, alcohol, methamphetamines, and nicotine).

Women recruited at Harbor-UCLA hospital and Cedars Sinai Medical Center are in the POE, PDE, and drug-free groups. The opioids used are prescription opioids. Women recruited from Cedars Sinai Medical Center have a simpler drug usage profile. Compared with women recruited at Cedars Sinai Medical Center, women recruited at Harbor-UCLA and TTC are younger and less educated and have lower incomes. The women recruited at TTC and Harbor-UCLA match the racial demographics better than the women recruited at Cedars Sinai Medical Center. To date, women recruited from Cedars Sinai Medical Center have a lower rate of adverse events; however, only one woman recruited from Harbor-UCLA completed the assessment. There is no difference in maternal health problems, depression, or anxiety scores between the groups.

To date, 313 COPE survey visits and 23 postnatal assessments have been completed. Remote biosample (i.e., blood, nails, hair, fecal) collection and online behavioral observation/assessments are ongoing.

The group developed an MRI-compatible crib, which allows imaging of infants during sleep. The prototype will be tested and modifications will be made as needed.

Using data from existing studies, the team has identified the impact of prenatal drug exposure on functional connections. Around 5 percent of whole-brain connections are affected by PDE, which is comparable to the combined effects of five critical factors (e.g., maternal depression) that are known to have implications on brain development. Another study identified heterogeneity of connections in brain-behavioral associations. The team is also able to make individualized predictions of behavioral outcomes (4-year IQ outliers) based on early imaging data and heterogeneity with high specificity and accuracy.

Biological and Environmental Contributions to Healthy Baby Development in Diverse Populations
Patt Levitt, Ph.D., Children's Hospital of Los Angeles (CHLA)

Dr. Levitt described progress throughout the COVID-19 pandemic. The working groups are Recruitment and Retention, Bioethics, Neuroimaging, EEG/Eye Tracking, and Non-Imaging Measures.

In response to COVID-19, the team developed hybrid protocols to capture data remotely, eliminated breast milk collection and eye tracking to reduce COVID-19 risks, began participating in the COPE study, revised onsite visits, and generated COVID-19 screening protocols and standard operating procedures for positive screens.

The team's recruitment partners include organizations—such as a private obstetrics/gynecology practice, a community pediatric network, neonatology groups, and a nonprofit organization—that have access to an ethnically diverse population that has a broad range of SES and is enriched for high-SU risk exposure. In-person recruitment has been limited in these partner organizations by COVID-19.

The study protocol has two workflows (default and alternate) to accommodate participants needs. The default protocol incorporates an initial COVID-19 screen, followed by consent, leg sensor placing, questionnaires, EEG, neurodevelopmental assessments, MRI scanning, and compensation. The alternate protocol also has an initial COVID-19 protocol and consent; however, the order of the assessments can shift depending on the status of the infant. Home visits are not allowed.

During the pandemic, the team conducted remote research with underrepresented minority high school students, worked with investigators to integrate remote platforms and wearable sensory technology, evaluated EEG microstates and pipelines, and studied dyadic interactions. One of the remote platforms the team is integrating with allows for both screening and e-consent and provides enhanced communication (e.g., video conference, notifications) with high-risk families. Motor development is being studied with a wearable sensor that assesses natural environment motor limb movement over 48 hours, variability in movement across days, and napping/sleeping and physical activity.

High-resolution EEG collection for source localization and EEG microstate detection is being optimized in collaboration with the University of Maryland and Boston Children's Hospital. EEG microstates are useful because they can be a proxy for the study of fMRI brain networks (i.e., auditory, visual, salience, and attention networks) and are sensitive to developmental changes. Because EEG microstates have been studied only in persons age 6 years and older, using this approach in younger children is a valuable opportunity for significant discovery. In addition, issues such as missing sensors and sensor motor/artifact are being considered. The group is evaluating automated pipelines for data collection in infants and developing an ERP task and automated demarcation of postural changes that generate artifacts.

Mother-infant dyadic interactions captured with mothers and infants of 2, 6, 9, 12, and 18 months of age during a session that involves play, still face, and reunion, are analyzed using a machine learning approach. This study is being done in combination with coding interactive behavior (CIB), which is sensitive to variations in interactive behavior due to multiple factors, including infant age, cultural setting, interacting partner, biological risks, social-emotional risk, parental factors, and intervention effects. In addition to gaining insight into the interaction (e.g., reciprocity), CIB allows investigation of the adult (sensitivity, intrusiveness, limit setting) and child components (involvement, withdrawal, compliance).

COVID-19 RESEARCH Data Blitz (02:14:29)

COVID-19 supplements were awarded to investigators across 17 different sites. The studies will yield the following data:

- COPE Study—longitudinal survey data on parents and infants

- Biospecimen collection—virus and antibody panels, stress, and epigenetics

- Additional assessments—qualitative interviews, home language/environment analysis, MRI/EEG brain structure and function, SU, anxiety, depression, and stress.

Longitudinal Evaluation of the Impact of the COVID-19 Pandemic on High-Risk New and Expectant Mothers
Lauren Wakschlag, Ph.D., NU; Moriah Thomason, Ph.D., NYUSM; Cynthia Rogers, M.D., WUSM; Alexandra Potter, Ph.D., University of Vermont Medical Center; Ashok Panigrahy, M.D., University of Pittsburgh Medical Center; Wei Gao, Ph.D., Cedars Sinai Medical Center; Alice Graham, Ph.D.; Hanna Gustafsson, Ph.D., OHSU; Patt Levitt, Ph.D., Children's Hospital of Los Angeles; Beth Smith, D.P.T., Ph.D., University of Southern California

The COPE Study is being performed across eight sites using a harmonized protocol to collect survey data to investigate the impact of COVID-19. The diversity in the incidence of COVID-19 positivity rates across the different sites gives insight into the geographic differences of pandemic impact on pregnant women and young children—survey results are available in the COVGEN site. The surveys, which investigate changes in components such as mental health, healthcare, and social support, are being administered domestically and internationally.

Additional data are being collected in a subsample of participants, including surveys responses, biospecimen samples (i.e., blood, nail clippings, hair, and saliva), and virtual mother-infant observations at 6 and 12 months of age. Neuroimaging (i.e., EEG, MRI) will also be performed in some participants. Behavior is being assessed using a still-face task, arm restraint, free play, cleanup, and a visual attention task.

Collaborative manuscripts are emerging with a variety of themes—within the COVID-19 pandemic context—including the geographic variability of disruption to perinatal care, maternal adaptive function, predictors of maternal concern on child's health, changes in social support of pregnant women and postnatal mothers, and heterogeneity in maternal perinatal symptom change.

Understanding the Effects of COVID-19 on Maternal Substance Use
Julie Croff, Ph.D., OSU

Investigators at OSU partnered with the 5-STAR Consortium to study social changes caused by the pandemic, focusing on individuals at low and high risk of SU during pregnancy or SUD. Participants complete the Epidemic-Pandemic Impacts Inventory (EPPI) and an in-depth interview. The study has overrepresentation of multiracial and American Indian/Alaskan Native populations and underrepresentation of African Americans.

In the EPPI, low-risk mothers reported experiencing a higher increase in mental health problems or symptoms than high-risk mothers, not being satisfied with changes in mental health treatment, and paying more attention to personal health than high-risk mothers. There were no significant differences in increase in use of alcohol or other substances. Because having children stay home during the pandemic is a stressor for individuals, SU was examined. Low-risk mothers reported an increase in use of alcohol and other substances, mental health problems not related to the disease, and overeating/eating unhealthy food. Responses to the in-depth interviews, which explored negative and positive aspects of social distancing, stress management, and past experiences, indicated that participants who experience early-life adversity or challenging life experiences exercise their resilience.

Planning for the HEALthy Early Development Study
Christina Chambers, Ph.D., M.P.H., University of California

The team added questions and data collection to MotherToBaby studies, which are built on a network of 14 sites that provide individualized risk assessments for exposure in pregnancy or lactation. Women are recruited for longitudinal pregnancy and lactation outcome studies.

For the pregnancy study, women who have/have not been exposed are enrolled in early pregnancy and placed in one of three cohorts; exposed, disease comparison, and healthy comparison. Three interim interviews are done during pregnancy and one outcome interview and medical record review are conducted postpartum. Follow-ups include a remote physical exam of children, a developmental assessment done at 1 year of age, annual pediatric medical record reviews, and a developmental assessment (3.5 to 5 years of age).

The protocol was modified to screen on COVID-19 symptoms, testing, and treatment at time of testing and throughout pregnancy and include COPE survey questions and antibody testing. In total, 581 unique women have been enrolled since March. Of these, 247 women met specific criteria (e.g., negative test, positive test, symptomatic, exposed) and 334 did not meet the above criteria (no COVID group). In addition, 953 women who were enrolled before the pandemic were used for comparison (prepandemic group). The team found alcohol use before recognition of pregnancy is common; however, alcohol use decreases after recognition of pregnancy—marijuana use follows the same trend. Stress and depression are higher in the pandemic groups than in the prepandemic group. A lower percentage of women in the pandemic groups completed prenatal tests. Outcome analysis is ongoing; preliminary data show positive-test and symptomatic women have increased risk for preterm delivery. Analysis of symptoms showed loss of taste, smell, and appetite were the only frequent symptoms in positive-test women. Determining whether women were infected during pregnancy will be important for outcome analysis.

In Utero COVID-19 Exposures and Neurodevelopmental Outcomes
Charles Nelson, Ph.D., Harvard University

The team aims to examine the prevalence of psychological distress in pregnant women with a confirmed COVID-19 diagnosis, examine the role existing high-risk environments play in the susceptibility of heightened psychological distress, and study the effects of prenatal distress and maternal illness/inflammation related to a maternal COVID-19 diagnosis on brain development. In addition, neural networks that may have been impacted by maternal COVID-19 infection and related stress during pregnancy will be characterized, and early neurodevelopment outcomes of infants exposed to elevated prenatal stress and trauma related to maternal COVID-19 diagnosis during pregnancy will be assessed.

COVID-19-positive and -negative mothers in the third trimester—recruited from Brigham and Women's Hospital, Massachussetts General Hospital, and Beth Israel Deaconess Medical Center—will complete maternal questionnaires and a health inventory. Following birth, (optional) MRI will be done on newborns. Infant EEG and behavioral task assessments will be done at 3 and 6 months of age.

Recruitment materials have been distributed at the three recruitment sites to begin enrolling women in the study. However, competition due to recruitment efforts of multiple studies has posed a challenge to engaging participants, particularly those who are COVID-19 positive and have psychosocial risk factors.

SU, Distress, and Coping in COVID-19 Positive and Negative Pregnant Women
Lynn Singer, Ph.D., Case Western Reserve University

The ultimate goal of the study is to determine whether SU during pregnancy increases vulnerability to COVID-19-related stressors. Aim 1 is to characterize the type, amount, and frequency of substances (prescribed and nonprescribed) used by pregnant women with and without diagnosis of COVID-19 in Northeast Ohio. Aim 2 is to

characterize the mental health symptoms, coping mechanisms, and social supports of pregnant women with/without a diagnosis of COVID-19. Aim 3 is to identify whether pregnant women with positive COVID-19 diagnosis differ from pregnant women without active disease in history of and current SU, SUD, mental health symptoms, coping mechanisms, and social supports.

The team is also aiming to determine whether SU is related to occurrence of and severity of COVID-19 by studying SU and SUD, mental health symptoms (using COPE measures), social factors (e.g., vaccine readiness and food insecurity), coping mechanisms, and social supports in the target recruitment population for Phase II.

To date, the team has developed electronic informed consent, submitted to the IRB, and identified COVID-19-positive women for recruitment. Next steps include recruitment of COVID-19-negative women and data collection. Deliverables include a report and a manuscript.

FL-DECADE COVID-19 Study
Matthew Gurka, Ph.D., UF

The team aims to understand COVID-19-related stress, anxiety, and mental health issues among pregnant and parenting women in Florida, focusing on racial/ethnic differences/disparities. The baseline survey, which includes COPE survey and family violence questions, is ongoing with pregnant women. Follow-up questions of women three months postpartum will include COPE questions and examination of vaccine hesitancy.

Women are being recruited through Healthy Start Coalitions across Florida and the OneFlorida Clinical Research Consortium. Women recruited through Healthy Start Coalitions will be mainly high-risk women whereas women enrolled through OneFlorida will most likely be in higher SES levels.

Diverse pregnant women (50%) and new mothers (50%) were recruited through Healthy Start Coalitions from both urban and rural areas. Of these high-risk women, 41 percent responded that their living environment has changed since the beginning of the pandemic; 43 percent stated the impact has been somewhat or very negative. About two thirds of women live with a partner and 10 percent have experienced a type of partner violence; over 50 percent reported the violence (controlling behavior) has worsened during the pandemic. SU through lifetime was also studied in Healthy Start women. A quarter of participants reported use of marijuana. Women also reported use of various other substances. In addition, 18 percent of women are currently receiving treatment for mental health concerns; 50 percent of these women reported mental health worsening during COVID-19. Future plans include integrating race and ethnicity comparisons into this analysis.

The team aims to evaluate the feasibility of using OneFlorida to characterize pregnant and parenting women who have tested positive for COVID-19. Thus far, a COVID-19 data table has been assembled and representation is being assessed.

The team is also determining the feasibility of remote data collection during pregnancy and postpartum. The LENA device will be used to capture home language environment, and home saliva samples from women and infants will be used to measure stress.

The Adverse Risk of Maternal Antenatal SARS-CoV-2 Infection on Child Neurodevelopment and Health Outcomes
Sean Deoni, Ph.D., Brown University

The overarching aim of this study is to determine how COVID-19 infection during pregnancy impacts fetal and infant neurodevelopment. Aim 1 is to compare brain and cognitive measures between infants with and without maternal infection. Aim 2 is to determine the impact of outbreak-related environmental stressors on infant neurodevelopment.

In addition to existing cohorts, the team will study two other cohorts: about 50 infants born to mothers with confirmed COVID-19 infection or without infection born between May and September 2020. The differential effect of antenatal infection and environmental conditions on infant development will be determined. A third cohort composed of about 1,500 infants born to mothers in the prepandemic era will be used for comparison.

Multimodal MRI, neurocognitive assessments, family and medical history evaluations, and biospecimen collection will be done at 3 and 9 months of age. To date, assessments on 3-month-olds are complete. Preliminary analysis shows children born to COVID-19-positive mothers have delayed myelination compared with children born to COVID-19-negative mothers. There is no evidence of increased prematurity in COVID-19 children. Dr. Deoni noted the sample population is highly skewed to Hispanic ethnicity.

Establishing Innovative Approaches for the HEALthy Brain and Child Development Study
Xiawei Ou, Ph.D.; Ashley Acheson, Ph.D., ACRI; Weili Lin, Ph.D., University of North Carolina, Chapel Hill; Stephanie Merhar, M.S., M.S.; Jennifer Vannest, Ph.D., CCH

Traditionally, HOME assessments are done in person at participants' homes. However, virtual administration of HOME, which will certainly be useful during the COVID-19 pandemic, has multiple advantages (e.g., accessibility increase, cost reduction) that would benefit studies past the pandemic era.

Aim 1 is to develop and test a virtual HOME inventory by testing 90 mother and infant/toddler dyads on virtual HOME and 45 dyads on in-person HOME. Secondary assessments (i.e., psychiatric symptoms, stress, and family interactions) will be done.

Aim 2 is to examine COVID-19 influences on parent-child interactions by using the COPE survey and the COVID-19 Exposure and Perinatal Experiences Study Survey.

The team plans to modify the HOME manual for virtual administration, conduct pilot virtual HOME sessions, finalize the Virtual HOME manual, train study staff, and collect and analyze data. Implementation of virtual HOME using web cameras and smartphones is being explored to facilitate assessments.

It is expected that virtual HOME will efficiently capture parent-child interactions, although full assessment of the environment may require additional questions. Virtual HOME may be optimal for the HBCD Study Phase II because accessibility will be increased and costs, burden, and safety risks will be reduced.

Meeting Wrap-Up (03:02:17)
Discussants: Michael Charness, M.D., Boston University; Terry Jernigan, Ph.D., University of California, San Diego; Cathy Spong, M.D., University of Texas Southwestern Medical Center

Dr. Michael Charness commended the teams' progress despite the challenges created by COVID-19. The study provides a great opportunity to understand the impact on children born during the pandemic. Researchers will need to design studies so that the effects of COVID-19 are distinguished from the effects of other adverse childhood events and developmental factors. Considering different populations will aid in studying COVID-19 effects—adverse events seem to be more prevalent in at-risk populations. Because populations affected by opioids overlap with populations most affected by COVID-19, it should be feasible to study both simultaneously. Compensation, which is valued more by at-risk subjects, could help oversample the population.

The transition to a virtual society must be considered; reaching out to patients at homes or creating spaces to engage in research are important for population studies. Effective sampling of populations and retention of subjects can be facilitated by considering participants' needs.

Dr. Charness indicated that difficult ethical issues, such as how to conduct observational studies that do not deliver services to needy subjects, are resolved through the humanity of research staff, who engage and gain trust of participants. It is the trusting relationships and the success of the research team that sustain longitudinal

studies. Compensation, which is more valued by at-risk subjects, could help oversample this population. The ABCD Study can assist the HBCD Study by sharing best practices and informing on propagation and standardization of training across sites. The insights into child development gained from the HBCD Study can be connected to the information learned from the ABCD Study. In addition, the HBCD Study infrastructure and resources can be leveraged to understand the impacts of both SU and COVID-19 on childhood development.

Dr. Jernigan indicated it is important to fully compensate families for their time and cover additional expenses. She further indicated that Phase II of the HBCD Study is an unprecedented opportunity to gain insight into a very poorly understood and early period in human development during which multiple superimposed and interacting developmental processes are ongoing. To fully observe and measure these processes, there is a need to monitor them with maximum temporal density in all domains. However, there are challenges, including burden, feasibility of sites, and budget. Thus, sponsors and teams must consider how to increase coverage during this period using resources such as sensor devices, virtual assessments, and collection of valuable biospecimens. She asked how NIH could aid this effort. Dr. Jernigan challenged investigators to consider how the approach to mothers and retention efforts might change if mothers are engaged to join a landmark study to contribute rare information about the first years of life.

Dr. Spong applauded the progress made and the COVID-19 funding provided by NIH. She added that observing interactions in the home environment may yield unexpected and valuable information. Obstacles can be viewed as opportunities that can be leveraged to gather more data.

Dr. Volkow noted the COVID-19 preliminary data presented indicate why these studies are important. She indicated that although engaging participants to contribute to the understanding of brain development is important, investigators must be responsive to funding agencies such as the Helping End Addiction Long-term[SM] (HEAL) Initiative. One limitation of these studies is funding; thus, investigators must help identify other ways to obtain resources and communicate the importance of these studies to those who make funding decisions.