National Institute on Drug Abuse

HEALthy Brain and Child Development Study

Spring PI Meeting

May 4–5, 2020

Day 1 Videocast: https://videocast.nih.gov/watch=37403

Day 2 Videocast: https://videocast.nih.gov/watch=37408

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Meeting Summary – Day 1

Welcoming Remarks

Nora D. Volkow, M.D., Director, National Institute on Drug Abuse (NIDA)
Michelle Freund, Ph.D., Director, HBCD Study, NIDA

Dr. Freund welcomed meeting participants and outlined the current status of the HEALthy Brain and Child Development (HBCD) Study-Phase I, co-funded by ten Institutes/Centers/Offices (ICOs) of the National Institutes of Health (NIH) and the NIH Helping to End Addiction Long-term℠ (HEAL) Initiative. In September 2019, 29 planning grants (HBCD Study-Phase I) were awarded across multiple states, and a kickoff meeting was held in October 2019 where five overarching working groups were formed. The working groups are:

1. Study Design
2. Imaging Assessments
3. Biospecimens
4. Ethics and Legal
5. Maternal, Neurodevelopmental, and Contextual Assessments.

During the two-day Spring PI Meeting, each grantee (or consortium) presented individual progress to date, and each working group chair/co-chair provided updates to highlight progress made in each area. Findings from Phase I will provide input for the Phase II study.

Pending funding and available resources, Phase II of the HBCD Study will include a consortium administrative core, data coordinating center, and biorepository in addition to individual study sites that will work in a coordinated way using agreed-upon protocols.

Dr. Volkow described the focus of the HBCD Study as one of the most important research endeavors in neuroscience: understanding normal brain development from the earliest point possible through early adolescence. Technological advances enable investigators to collect, integrate, and analyze imaging and other data to achieve this goal. Phase I of the HBCD Study will help document and demonstrate the feasibility and value of this project.

Funding for Phase II of the HBCD Study is pending. The HBCD Study receives half of its financial support from the NIH HEAL Initiative℠ and half from NIH ICOs interested in development. Currently, there is no firm commitment of NIH HEAL Initiative℠ dollars for the HBCD Study. Dr. Francis Collins, NIH Director, has charged all NIH HEAL Initiative℠ supported projects with considering ways to reduce costs, and Dr. Freund has been developing alternative budgets and scenarios that would enable the HBCD Study to move forward without impacting the sample sizes required to achieve sufficient power to meet the overall Study goals. This may mean prioritizing certain types of data acquisition, reducing scan frequency, or otherwise simplifying the Study so that it can answer the most important research questions (i.e., What is the trajectory of normal development of the human brain?).

Dr. Volkow also encouraged Phase I investigators to consider how COVID-19 has affected the Study and explore ways to demonstrate the power of their networks by documenting the impact of COVID-19 and related stressors on brain development.

Study Design Working Group Report

Amy Elliott, Ph.D., Avera Health
Moriah Thomason, Ph.D., New York University School of Medicine (NYUSM)

The purpose of the Study Design Working Group (SDWG) is to evaluate and summarize design considerations that can inform the design of the longitudinal observational HBCD Study. HBCD focuses on answering two central questions: (1) What are the developmental effects of prenatal opioid and other substance use (SU) exposures on children from birth through middle childhood? (2) What are typical or normative developmental trajectories for children from birth through middle childhood?

Question 1 (Q1 Exposures) reflects multiple etiological questions and requires consideration of confounds and selection bias. Question 2 (Q2 Development) is more descriptive in nature and emphasizes generalizability. Although Q2 provides a context for interpretation of Q1, each question brings its own distinct design considerations that inform sampling strategies, measurement strategies, and consideration of Study costs as well as site capacity and catchment areas. The design should enable comparability of a representative sample for an identified source population and provide guidance on critical representative factors. Sites must be able to collect aggregate information on those factors for their entire source population so that frequencies in their samples can be standardized to the source parameters.

Through discussion, the SDWG concluded that the Study is unlikely to enroll many participants who have single drug exposures. It is important to include non-substance-exposed individuals from similar backgrounds (e.g., race, ethnicity, socioeconomic status [SES]) and those from lower risk environments. Long-term effects of early adverse experiences or exposures on neurodevelopment cannot be understood without comparison to a normative sample.

The SDWG made the following recommendations:

- Enrollment before or near birth is paramount to achieving the objective centered on prenatal exposures.
- Recruitment protocols should be optimized for regional variation, be informed by clear understanding of contextual legal or policy regulations, and address both primary study objectives. Recruitment protocols that integrate with local services, engage stakeholders, and/or build on existing resource infrastructure will achieve optimal participant engagement and maximize longitudinal retention. It is important to identify recruitment success stories and barriers, and apply lessons learned.
- An articulated plan for participant engagement and long-term retention is a key component of study design. Bridges must be built within the community to support participants and the project.
- For Q1, creating prespecified recruitment groups is discouraged; flexibility is needed for powered comparisons of multiple causal etiologies. Sample size should be determined based on achieving these, including expected attrition at later years of the study. Q2 requires an entirely different design and sampling strategy for a representative sample that emphasizes generalizability.
- Sample size determinations should be based on expectations about developmental variation, data quality and completeness, and reliability of measurements.
- Study design and power analyses should account for group and temporal differences in attrition.
- Ensuring that sites can meet Study milestones will require accounting for sample size in the model for assessment frequency; experience with high-risk families; proposed research methodology and core protocol elements; the ability for high-throughput participant testing; and strong centralized coordination to ensure that sites can meet Study milestones.

Discussion

The SDWG considered enrolling a population representative sample and oversampling for high-risk individuals but acknowledged that it would be expensive. Working Group discussions around attrition were based on prior experience and evidence-based models on attrition.

The possibility of limiting the study to a single research question was discussed. Ultimately, the decision will depend on what is practical to accomplish with available funds. Determining feasibility will require understanding the power requirements for each question and the associated costs. Development can never be separated from the environment.

Participants briefly discussed to what extent it is essential to recruit early in pregnancy. There was some debate as to the validity of retrospective accounts of exposures.

Grantee Presentations

HEALthy ORCHARD

Daniele Fallin, Ph.D., Johns Hopkins University

Dr. Fallin outlined progress on HEALthy ORCHARD aims and reorganization of local working groups to align with national working groups.

The Recruitment and Retention Working Group was divided into three subgroups: Qualitative Pilot Work; Ethical and Legal; and Methods Considerations. Scripts and guides have been created for focus groups with women in the community and in-depth interviews with diverse stakeholders representing maternal and child health service organizations, obstetric and SU treatment providers, and social services. Due to COVID restrictions, data collection must shift to digital recruitment and collection, offering an opportunity to incorporate COVID-related questions.

The Ethical and Legal subgroup focuses on identifying and developing strategies to address ethical challenges and legal and policy issues associated with recruitment, retention, data collection, and dissemination. Examples of legal and policy issues include reporting laws, interpretation of certificate of confidentiality laws, and implications for data linkages and data sharing across medical, government, and community entities.

The Methods Considerations subgroup focuses on developing recruitment and retention protocols, including deliberating on design suggestions for the national strategy and creating design plans/feasibility for the local strategy. The work involves identifying recruitment partners, setting target numbers, testing feasibility and acceptability of strategies, and considering legal barriers and memoranda of understanding (MOUs).

The Non-imaging Assessments, Neuroimaging, and Biosampling Working Groups are populating a data collection grid for mother and child to serve as a framework for strategy consistency. Each strategy includes working principles around data collection and a list of constructs over time, and annotating these by scientific rationale for inclusion, feasibility, and acceptability (i.e., timing, burden, and ethical considerations such as privacy).

The Non-imaging Assessments Working Group is interested in factors that account for individual differences and heterogeneity in neurobiological correlates of psychopathology. These assessments offer an opportunity to ask COVID-related questions that probe infection, health, psych/SU, and stress.

The Neuroimaging Working Group is working with other imaging groups to construct imaging acquisition protocols across scanning platforms and to minimize scanning time and improve motion correction. The Biosampling Working Group is using the same framework for strategy development.

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

Dr. Levitt described progress on local project aims and activities. Partnerships have been established with clinical and community stakeholders. Current long-time partners are engaged in various kinds of research and are connected to diverse populations in terms of ethnicity, SES, and risk of SU exposure. They include an OB/GYN practice that serves low-income families and is a buprenorphine provider for pregnant women, a strong neonatology group, a large non-profit organization for families that have children with special needs, a community pediatric network, and a large non-profit community provider.

Development and incorporation of bioethics training is an important objective. California has no requirement to report parental SU to the Department of Child and Family Services (DCFS) independent of concern for child abuse and neglect. Thus, the project's standard operating procedure (SOP) centers on concerns for the welfare of the child related to failure to thrive, abuse, and/or neglect, including exposure to domestic violence and maternal suicide ideation. In January, all CHLA team members received training on child abuse and implementation of the SOP.

The community advisory board (CAB) advises on how to answer key questions such as whether to include or exclude preterm infants, how to handle missed visits, and how to minimize participant burden while maximizing measurement during sensitive periods. In Dr. Levitt's experience, the period of highest attrition is between the first and second visit; once relationships are established, retention tends to be quite high.

The project has accumulated an inventory of resources for participants, including referrals to WIC (the Special Supplemental Nutrition Program for Women, Infants, and Children), SU treatment, and other community organizations.

The research environment is as flexible as possible. Staff are available for evening/nighttime magnetic resonance imaging (MRI) scanning and on weekends, which is especially important for working families. In addition to expertise in biosample measurement, team members have experience with advanced signal processing applications for eye-tracking, wearable sensors, and electroencephalogram (EEG) as a measure of brain network activity, as well as automated head pose signal processing for determining response and engagement during mother-child interaction.

Discussion

California is not the only state where low-SES populations are more likely to be tested for drug use in the perinatal period and more likely to be reported to DCFS. It would be helpful for the ethics training to include ways to counter implicit and explicit racial and SES bias by personnel. Slides and a video of the training are available for sharing.

Ethics/Legal Working Group Report

Pilar Ossorio Ph.D., J.D., University of Wisconsin (UW)
Alexander Capron, LL.B., M.A., University of Southern California (USC)
Seema Shah, J.D., Northwestern University (NU)

Dr. Ossorio noted Working Group members and others contributed to an ethics guideline that is available to HBCD Principal Investigators (PIs) and requested feedback from HBCD sites. The Ethics/Legal Working Group (ELWG) has five writing groups, with each focusing on a topic critical to HBCD: embedded ethics; consent, permission, and assent; overlapping vulnerabilities; use of pervasive sensing and monitoring; and privacy and data sharing.

ELWG discussions have focused on legal issues and what a formal legal analysis can do for each site. Many states are not fully compliant with the Comprehensive Addiction and Recovery Act (CARA), and there is high variability in

the way the law is applied within states and counties. While valuable, a formal analysis cannot provide information about attitudes and approaches of local law enforcement and prosecutors. Local expertise is necessary. Further, it is vital to know the policy of one's institution; some institutions require reporting even when the law does not.

Projects should pay careful attention to language of the law specifying mandatory reporters (e.g., midwives, birthing center staff). Researchers typically do not meet the definition for mandatory reporting. Reporting results of a mother's drug test is often not mandatory, but reporting results of a baby's drug test may be. Some members report that state officials want the Study to retain children when they are in foster care; this presents some challenges, but none are insurmountable.

The Working Group has not had in-depth discussion of project obligations to participants in terms of services. Researchers are not acting in their role as healthcare providers. Duty to help may be grounded in theories of reciprocity or solidarity and is tied to the concept of baseline services owed to any participant. Other issues include justice concerns about inconsistencies between types and levels of services available at different HBCD sites.

Provider interpretation of CARA has an impact on how they treat or screen pregnant women. People have their own understanding of legal rights and responsibilities and act on that, no matter whether their interpretation is consistent with what the statutes say or lawyers advise. A formal legal analysis could help inform investigator training and be used to educate Institutional Review Boards (IRBs).

Discussion

The Working Group has tried to focus on the broader, big-picture questions that cut across what the sites currently are doing.

Participants asked for recommendations related to type of sample or timing of analysis and reporting requirements. Some state laws specify reporting based on blood, meconium, or sputum samples but not other types of samples. In states where testing of a baby has triggered mandatory reporting, many institutional lawyers or policies expect researchers to report anyway. Projects need to clarify these institutional policies in advance.

Grantee Presentations

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

Dr. Gurka outlined progress on aims of the FL-DECADE study.

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 connecting to the community through a summit and focus group activities.

A FL-DECADE summit entitled "Legal, Ethical and Pragmatic Considerations for a Prospective Cohort: Minimizing Risks & Maximizing Benefits" (see https://opioid.cme.ufl.edu/) will build on two UF-led summits on early childhood. Due to COVID-19 restrictions, the summit has been moved to a virtual platform. On May 8, a personal experience panel of mothers in recovery, foster mothers, and kinship relation foster mothers will be followed by a discussion about application of laws. Legal scholars and representatives from the Department of Children and Family and support programs will participate. The May 15 presentations will include an overview of relevant state programs and breakout groups on mitigating risks and providing benefits, understanding changing family dynamics, and bias and stigma. Breakout discussions on May 22 will explore areas of future research.

To date, two focus groups have been conducted at an inpatient Mother's Intensive Supportive Treatment (MIST) program. In addition to robust discussions on incentives, participants indicated that they have no issues with

sharing information about SU and adverse childhood experiences (ACEs); researchers must ensure privacy and confidentiality of participants; continuity of research staff will build trust over a long period of time; and face-to-face interactions with researchers are preferred. There was strong resistance to home visits. Due to COVID-19 considerations, the focus group protocol is being revised for delivery via Zoom.

UF has established strong communications with the Florida Department of Health, the Department of Children and Families at the state and local level, and the Healthy Start Coalition.

For the recruitment assessment, UF has received approval to conduct a survey of health systems and OB/pediatric clinics in the OneFlorida clinical data research network in the late summer. The survey will gauge interest in participating in Phase II, characterize clinics, and assess MRI and other capabilities. UF also is building close relationships with community partners, including Adolescent Brain Cognitive Development (ABCD) investigators at UF and Florida International University, as well as with the Clinical and Translational Science Institute (CTSI) imaging core.

The feasibility study has been delayed due to COVID-19 restrictions. Planning is moving forward with the addition of some COVID-19 work and testing feasibility of virtual assessment. The team began working with the IRB to navigate legal/ethical issues important for Phase II but stalled due to COVID; these activities will be revisited.

The Brain Begins Before Birth (B4) Midwest Consortium

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

Dr. Rogers summarized progress on B4 aims at the WUSM site.

The assessment methods aim is to generate an informed protocol for exposure, imaging, and other childhood developmental and psychosocial context assessments. Key deliverables are extensible and reproducible exposure, development, and neuroimaging protocols, including community-based assessments applicable across institutions, settings, and age groups, with emphasis on prenatal stages through age 5 years. Biological samples include hair, blood, urine, saliva (mother and baby), and stool samples (mother and baby). Progress on this aim includes creation of an assessment protocol for SU and psychosocial factors and a schedule for assessment collection, as well as adoption of established MRI protocols from other studies.

WUSM has worked closely with other collaborators to incorporate innovative compressed sequences into an established multimodality neonatal protocol for testing. Compressed sequencing can reduce scan time with comparable quality, and motion navigation increases motion resistance. WUSM obtained high-quality MRI scans in infants with neonatal abstinence syndrome (NAS). The team will re-pilot infant functional near-infrared spectroscopy (fNIRS) as another potential imaging modality.

The B4 recruitment and retention aim is to model and pilot multiple pre-/post-partum recruitment and retention strategies using a mixed-methods, community-engaged approach. Key deliverables for this aim are integrated recruitment and retention strategies and a toolkit catalog that details methods applicable across settings and study designs and accounts for regional and individual differences. Recruitment strategies for perinatal women have been established.

At WUSM, progress includes establishment of a three-stage enrollment process in two study arms: the Standard Care and u-MAT-R App. Each stage targets recruitment from a different clinic or department with the objective of maximizing recruitment effectiveness and addressing challenges. Recruitment includes digital consent and recruitment of perinatal women using electronic medical records (EMR) and clinic staff. Infants with NAS or neonatal opioid withdrawal syndrome (NOWS) are identified via EMR.

Dr. Shah described progress at NU. Recruitment flyers have been drafted and vetted. A plan to use eye-tracking to measure visual attention to various flyer features is on hold due to COVID-19. The current plan is to have

participants describe their perceptions of the flyers and answer questions about their ability to find and understand the information provided.

The legal and ethical aim is to use a mixed-methods approach to examine research and clinical implications of state-level differences in access and participation to create strategic solutions for identified obstacles. Key deliverables include best practices recommendations and a manuscript on study design.

Progress on the legal/ethical aim includes development of a mail survey about how laws affect care provided and willingness to refer patients to research; development of a qualitative interview questionnaire to obtain perceived barriers and best practices for research from community stakeholders and researchers studying SU in pregnancy; and establishment of collaborative partnerships with stakeholders and the Florida HBCD project.

Several NU and WUSM studies will be combined to pool the cohorts and look at predictors of developmental outcome. In addition, a B4 synthetic cohort will be used to determine different risk factors for developmental outcomes and inform methodologic decisions in HBCD.

Biospecimens Working Group Report

Ludmila Bakhireva, M.D., Ph.D., M.P.H., University of New Mexico (UNM)
Karen Grewen, Ph.D., University of South Carolina

Drs. Bakhireva and Grewen discussed the process and guiding principles of selecting biospecimens of interest and presented an overview of essential and recommended data elements and analytes of interest. The ultimate goal of the Biospecimens Working Group is to characterize the exposome from the prenatal to early childhood stages. The first domain is targeted analysis of substance exposures, including drug use, prescription drug misuse, medications for opioid use disorder (e.g., methadone, buprenorphine), and tobacco. The second domain is prenatal and postnatal maternal nutrition, environmental exposures, comorbidities, and microbiome. Markers of biological response comprise the third domain. The National Institute of Environmental Health Sciences (NIEHS) Children's Health Exposure Analysis Resource (CHEAR) Program served as a starting point, along with review of protocols from other successful multi-site cohort studies such as Environmental influences on Child Health Outcomes (ECHO).

The Working Group developed guiding principles for distinguishing between essential and recommended data elements. Considerations included balancing scientific rigor and risk to subjects, cultural acceptability, invasiveness, sensitivity and specificity, detection window, site expertise and available infrastructure with alternative specimens if recommended specimens are not feasible, ease of collection and processing, and stability.

The Biospecimens Working Group has shared an Excel workbook that lists the essential and recommended biomarkers for each domain and provides the rationale for their use.

Essential data elements for mothers include pre-birth blood, urine, saliva, and fingernail clippings; blood and urine at delivery; and saliva during the neonatal period. Saliva can be used for genetics, epigenetics, co-exposures, and drug exposures. Essential data elements for children include urine and cord tissue (alternative: meconium) at delivery (hair and fingernail clippings as alternatives for sites that cannot attend delivery); saliva at less than 1 month of age; urine and saliva (alternative is stool) between 2 months and 1 year of age; urine, saliva (alternative is stool), teeth, and nail clippings between 1 and 5 years of age; and saliva, teeth, and nail clippings between 5 and 10 years of age. Recommended data elements for mothers include vaginal swab, expired air (breathalyzer), stool, fingernail clippings, breast milk, and hair. Recommended data elements for children include cord blood, placenta, fingernail and toenail clippings, blood spots, and hair.

Whole blood, plasma, and serum provide information for environmental contaminants, nutriture, epigenetics, and tobacco and nicotine exposure. Saliva provides DNA as well as information about the oral microbiome,

epigenetics, and co-environmental exposures. Windows of detection for various biospecimens are as follows: fingernail clippings, up to 6 months; hair, up to 3 months; urine, 2 to 3 days; meconium and cord tissue, up to 20 weeks. Self-collected specimens include vaginal swab, deciduous teeth, saliva/buccal swab, stool, and nail clippings.

Substance exposure subgroups include opioid biomarkers, ethanol biomarkers, and direct or second-hand tobacco. The co-exposures subgroup includes environmental contaminants, nutriture, and the microbiome. The genetics subgroup includes genomic, stress, and inflammation assays.

Members of the Biospecimens, Legal/Ethics, and Study Design Working Groups recently formed a Tribal Communities Special Interest Group to identify key principles and challenges and propose solutions when working with American Indian communities. It is important to acknowledge historical considerations, cultural heterogeneity, confidentiality, biomarker banking, genetics, and targeted versus broad hypotheses.

Discussion

There may be interest in identifying markers from alternative nicotine delivery systems (e.g., vaping, nicotine replacements). Dr. Grewen noted that she has measured carbon monoxide from individuals who use these products.

Grantee Presentations

Planning for the HEALthy Early Development Study

Christina Chambers, Ph.D., M.P.H., University of California, San Diego (UCSD); Ludmila Bakhireva, M.D., Ph.D., M.P.H., UNM; Clair Coles, Ph.D., Emory University; Julie Croff, Ph.D., Oklahoma State University (OSU); Lynn Singer, Ph.D., Case Western Reserve University

Dr. Croff presented an update for the 5-State Alliance for HEALthy Early Development Research (5-STAR) Consortium. The Consortium has broad geographic and strong racial/ethnic diversity and a history of longitudinal studies with SU exposure and a focus on recruitment and retention of focus groups.

5-STAR aims to establish collaborative teams to work toward a Phase II prospective study of human development from prenatal life through ages 9–10; test feasibility at each site to implement common protocol elements for neuroimaging, neurodevelopment, assessment of exposure, and innovative technologies in the first 24 months of life; and exchange strategies, findings, and recommendations based on the above aims with key partners.

5-STAR feasibility testing accomplishments include focus groups and interview data collection; preparation of a common protocol and initiation of developmental assessments prior to COVID-related delays; and preparation of common protocols for neuroimaging and innovative technologies before shelter-at-home orders were issued.

Qualitative research is being conducted to determine acceptability of an explanatory research video, understand participant preferences in marketing Phase II of the study, and understand information families need to make informed decisions about joining the Phase II study. Preliminary qualitative results were derived from an analysis of focus groups and one-on-one interviews. Topics included context of high-risk participants, motivation to participate, information needed to decide about participating, research concerns, and incentives and best marketing strategies/channels/tools. Lessons learned and best practices derived from these preliminary results include:

- Understanding underlying motives, concerns, and needs of participants is critical for recruitment and retention in longitudinal studies.
- Incentives must be adequate to address barriers to participation.
- Recruitment approaches must appeal to altruism and emphasize how participation can bring benefits to individuals, families, and communities. Return of some research findings is a key benefit.

- Explainer videos should be expanded to include testimonials from other participants and researchers and incorporate branching logic to address questions or concerns.

Most of the concerns for the baby were related to potential harm from biospecimen collection and imaging safety.

The three sites that have extensive experience with MRI imaging of infants or young children share expertise with the other two sites. The two ABCD sites provide expertise in coordination and harmonization. All five sites have extensive experience with longitudinal studies and examination of children in the study age range.

Harmonization efforts include aligning protocols and identifying a core protocol. Site-specific sequences of interest include arterial spin labeling (ASL), magnetic resonance fingerprinting, and spectroscopy. Investigators have met with three major MRI manufacturers for harmonization of scan parameters across platforms. The Oklahoma site is purchasing a research-quality 3T MRI, and several sites are upgrading to the newest scanners.

All five sites plan to collect pilot data on infants at three different ages (delayed due to COVID-19); data will be shared to evaluate quality. Additional analyses will be conducted to estimate sample size, and HBCD investigators will continue to discuss strategies and procedures to optimize outcomes.

As the study moves forward, it is understood that new substance exposures will emerge, and polysubstance use will be common among participants. Polysubstance use in pregnancy will be an important study design consideration.

Over the next six months, 5-STAR plans to complete qualitative data collection and analyses, relaunch neuroimaging and developmental feasibility assessments, and implement a crib sensor feasibility project.

Discussion

There was brief discussion about co-exposures to prescription medications in the general population as well as among women with SU disorders.

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 National Research Hospital; Charles Nelson, Ph.D., Harvard University; Nathan Fox, Ph.D., University of Maryland

Dr. Elliott presented an introduction to the Consortium network and current progress. All sites have established relationships with a broad range of partners from law enforcement, court authorities, family and child services, state entities, tribal members, pediatric clinics, and hospitals.

Lessons learned from community involvement include:

- The web of services, government agencies, charities, and legal considerations is complex and communication should be a priority.
- Opioid usage is complex and spans the SES spectrum; multiple-drug exposures make having a single control group impractical.
- Working in remote rural communities presents challenges for effective recruitment and retention as well as data, biospecimen, and image collection.

The Consortium is leveraging new pregnancy cohorts (developed in ECHO) as well as large, extant longitudinal studies for testing elements and protocols. EEG protocols have been disseminated across all the sites.

Dr. Blair described testing of a novel remote recruitment strategy using Facebook advertising. A first pass that targeted a broad list of search terms produced responses from many more healthy individuals than would be needed. Subsequently, investigators used a list of SU-relevant search terms.

Drs. Fox and Deoni presented Consortium efforts to bring the lab to the community, which is a guiding principle for the Consortium. Dr. Fox described mobile technologies as a way to reach participants in remote rural locations. Showing hard-to-reach families how to use a portable EEG system in the home would help build trust and increase their willingness to come to the clinic for a subsequent MRI. The EEG system needs to be portable, easy to use, and quickly set up in a home setting by individuals with minimal training. The concept has been applied in the Baby's First Years project using an Enobio System. Results include an 80% success rate for capping, a 95% success rate for recording five minutes of data, and an 84% overall usable data rate.

Dr. Deoni described additional ways the Consortium is pushing the limits of home-based assessment. The Epilog System is a wearable EEG that can capture beta and delta activity, sleep spindles, and autonomic activity; has a battery life of up to 20 days of continuous recording; and is reusable, disinfectable, easy to apply, and returnable by mail. The device has been tested in adults, adolescents, and toddlers. Testing with infants is in process.

Other wearable technology offers the potential for remote, non-invasive data collection specific to environmental exposures known to impact development (e.g., air quality, light exposure, family environment, physical activity, heart and respiratory rate). However, available devices often are bulky, not size-appropriate for infants, and expensive. Working with a Silicon Valley company, the Consortium is developing a silver-dollar-sized wearable device that integrates multiple measures and includes EEG and electrocardiogram (ECG) sensors with the capability of capturing one month of data. If successful, the next step will be to convert the device into a printable tattoo that adheres to the shoulder and uploads data to an iPhone.

The Consortium is exploring ways to extend the mobile technology concept to make all imaging modalities, including MRI, truly mobile and to bring state-of-the-art equipment to remote communities. Mayo Clinic and GE have developed a smaller head-only or pediatric scanner that maximizes gradient strength and optimizes the fidelity and quality of diffusion for imaging; the equipment weighs about 1.5 tons, which is the towing capacity of a Ford® F-150 pickup truck. One could equip a trailer and park near an electrical hookup. Perhaps the equipment could be reduced to fit into an even smaller vehicle and pull a trailer behind it to provide energy to run the equipment.

Building on the idea of the home EEG assessment, the Consortium is looking at a purely mobile MRI scanner that can be taken anywhere without safety concerns. The group has tested a mobile system developed by Hyperfine that uses low field strength and low gradients. The device does not provide the fidelity of the scanners used in medical facilities, so there is more work to be done.

The Consortium has focused on how to optimize quantitative and qualitative imaging across field strengths to improve resolution, reduce acquisition times, and demonstrate equivalence with conventional acquisitions. Through participation in ECHO, the group can access extant data for about 1,200 children that provide insights about changes associated with cognitive function; variability across the population; and various demographic, socioeconomic, *in utero* substance exposure, and SU variables that have an impact on development and function.

Discussion

There was discussion about different attitudes toward home visits. People in Providence, Rhode Island, did not want investigators coming into their homes. At other locations, participants have been more accepting of home visits. Baby's First Years focus groups have provided feedback to support at-home EEG.

Participants asked about fidelity variation concerns when some sites use at-home EEG and others do only lab-based EEG. The difference between the two systems is the number of electrodes used; that is, the home system has 32 channels and the lab system has 64 or 128 channels. When comparing within the same child, the number of electrodes from the systems look similar.

MRI-related claustrophobia has not been an issue. Children do not go far into the bore. When using the Hyperfine equipment, most of the children have been awake.

Participants asked about ensuring privacy when using Facebook for data collection. Dr. Blair clarified that Facebook provided a way for individuals to express interest in the study; no data were collected via Facebook. The ad included a click-through button that took viewers to the Boys Town website, where they provided contact information and a member of the research team followed up.

The chip device in the sensor technology is encrypted. Researchers do not have access to the raw audio feed; they analyze results from the device.

Promoting Resilience in Children: Protocol Development for a Birth Cohort Study to Access Factors Impacting Neurodevelopment

Andrew Alexander, Ph.D., UW; Pilar Ossorio, Ph.D., J.D., UW; Ellen Goldstein, Ph.D., UW; Douglas Dean, Ph.D., UW

Dr. Goldstein presented a summary of progress on Project Aim 1: Finalize the recruitment and retention protocol for the birth cohort study. Progress includes synthesizing existing knowledge relevant to HBCD recruitment and retention, engaging with stakeholders to better understand barriers and facilitators to engagement among opioid-exposed women, and testing selected recruitment and enrollment strategies in a pilot study of women with addiction during the pregnancy/postpartum period.

A literature review on recruitment and retention identified recruitment facilitators, including partnerships with clinics, outreach to community and government agencies, and relationships with key community members, as well as recruitment barriers, including participant reasons for refusal (e.g., invasive procedures) and protocols yielding unrepresentative samples.

A survey of experts reported key incentives (transportation and childcare services and basic goods), retention facilitators (flexibility and reduced burden, a successful retention protocol), and study success factors (building trusting relationships between study teams and participants).

A stakeholder advisory committee (SAC) that included representatives from Wisconsin state departments, professional organizations, and treatment providers was established and participated in brainstorming sessions on barriers that prevent pregnant women with SU disorders from being engaged in research. The top three identified barriers and possible solutions were as follows:

1. Shame/fear of judgment – Proposed solution: built-in, ongoing feedback from target population
2. Fear of legal consequences – Proposed solutions: revised state/federal laws; focused efforts in states without severe risks
3. Lack of trust in confidentiality – Proposed solutions: recruitment through trusted partners, offer of peer support, relationship building.

In addition, stakeholders provided guidance on participant incentives, ways to alleviate concerns, and how to present information. They also assisted with development of a scripted guide for qualitative focus groups and in-depth interviews with women with lived experience of addiction during pregnancy and/or motherhood.

The group plans to pilot test recruitment strategies. Women with addiction will be recruited using two methods: one with peer support and one without peer support. The peer support group will have state-certified peer support specialists who will receive additional pregnancy training.

Dr. Ossorio presented a summary of progress on Project Aim 2: Ethical and legal groundwork for HBCD Phase II. Progress includes a systematic literature review of issues related to cohort studies; informant interviews on issues related to opioid use; and an ongoing 50-state analysis of HBCD Phase II-relevant statutes, cases, attorney general opinions, and outcomes. The literature reviews and interviews have been compiled, reviewed, revised, and circulated.

To date, coding has been completed for 12 states. A written report will be prepared and converted into a searchable website, which will be beta tested in the fall to determine the types of summaries and visual representations of greatest value to HBCD investigators.

The group has obtained two MOUs. Relevant types of contract clauses from other contexts are being collected. The group began organizing agreement negotiation meetings; these now will be held in a virtual format.

The group has contributed to analysis of information from SAC meetings. Two interviews have been completed, and remote focus groups are planned.

Dr. Dean presented a summary of progress on Project Aim 3: MRI protocol development. Using a protocol from a previous study, investigators collected standard structural weighted images, resting-state functional MRI (fMRI), and diffusion imaging in infants (1 month old) and toddlers (2 years old). All sequences were acoustically de-rated to facilitate scanning during natural sleep, which increased total acquisition time to about 45 minutes. For infants, high success rates were achieved for structural weighted images (93% for T2 and 87% for T1). The diffusion imaging success rate was 89%, and resting-state fMRI achieved a success rate of 65%. Toddlers at 2 and 3 years of age were the most difficult to scan; success rates improved if the children remained asleep throughout the scan.

The group focused on developing new techniques for robust structural imaging using a retrospective motion correction method called MPnRAGE to retroactively correct for intra-scan motion. Structural imaging scans take seven to nine minutes, which may be too long for early childhood. Accelerated methods produced good results in about two minutes and with comparable quantitative measurements. The group is working on acoustical attenuation and is piloting ways to look at cortical microstructure using quantitative T1 measurements.

The group has developed multiple protocols on a GE MR750 scanner, testing different resolutions and varying numbers of diffusion directions. Investigators are trying DESPOT1, DESPOT2, and mcDESPOT approaches for relaxometry and piloting other methods for three-dimensional synthetic MRI and compressed sensing.

Investigators have experimented with various data analysis pipelines, including a recent release of the Infant Freesurfer connectome pipeline. The quality of subcortical segmentations is good, but the cortical segmentations need improvement.

The team has developed a novel task that presents multiple auditory, visual, and spatial location conflicts throughout the task for testing short-term working memory and activating cortical responses for conflict processing.

The group is collaborating with other teams on a feasibility study to train team members with limited experience using fNIRS with infants and toddlers. Existing fNIRS tasks and protocols will be used.

Discussion

Participants discussed experience using earmuffs for sound attenuation during imaging. Investigators reported using mini earmuffs that have some noise canceling options; mini earmuffs embedded in large headphones; and a combination of ear plugs, mini earmuffs, and headphones through which music and comforting sounds are played.

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 summarized progress on HEALthy BCD aims, including team building, recruitment and retention, imaging, and data analyses from ongoing projects. The team comprises seven major hospitals/institutions and nine geographically distributed study sites.

Progress on recruitment and retention includes two semi-structured focus group sessions that were conducted with a total of 12 women. Participants expressed distaste for the terms *home visit* and *social worker*. Alternate terms for *social worker* include *case manager*, *case specialist*, or *case supports*. Key participant recommendations included:

- Importance of confidentiality
- Characteristics of the primary contact person (consistent, non-judgmental, trustworthy, understanding, and ability to connect participants to appropriate resources)
- Appointment/scheduling flexibility, including weekend and evening hours
- Assistance with transportation needs
- Refreshments/baby formula at visits
- Child-centered gifts
- Intermittent raffles, photography sessions, and holiday parties/annual gatherings
- Mental health services/counseling/therapy sessions for family members as well as pediatric doctors/care.

Dr. Gao summarized current recruitment and retention information. Out of 21 mothers who were recruited during pregnancy, 20 have maintained contact for five to eight months, 16 have delivered, and 3 have completed their two-week visits. Two-week visits for 13 participants were postponed due to COVID-19.

Dr. Gao outlined the overall design, which includes four patient groups recruited from either Cedars Sinai Medical Center or Tarzana Hospital:

1. Mothers using opioids alone or with other drugs (POE)
2. Mothers using drugs other than opioids (PDE)
3. Matched drug-free high-risk controls who have other risk factors
4. A representative sample (RS) of individuals who may overlap with one of the above three groups.

To date, women recruited from Cedars Sinai have a much simpler drug usage profile than women recruited at other sites. Compared with women recruited from Cedars Sinai, women recruited from Tarzana are also younger and have a lower income, higher rate for maternal health problems, higher rate for adverse childhood events, and higher depression and anxiety scores. This speaks to the need to recruit geographically matched control samples from the delivery hospital sites.

Contact with some women in the POE and PDE groups was lost at two critical time points: (1) treatment facility change or premature discharge, and (2) after delivery. Contact was restored with some after multiple contacts with family members, friends, case managers, and the like. In general, retention of women in the POE and PDE groups has required much more effort than for women in the RS group.

Dr. Gao noted that preliminary results based on 120 unique subjects with 181 unique datasets were similar for the different groups. Subtle localized changes indicate that a larger sample size is needed to detect change.

Next steps for the project include a second recruitment round, imaging with novel correction strategies, and retention efforts to build relationships during treatment facility stays.

At the time of this meeting, a COVID-19 supplement involving six other sites had been approved for funding. Supplement aims include assessing the impact of COVID-19 stress on pregnant and postpartum parents and their infants; advancing understanding of risk moderators; and building a COVID-19 perinatal biospecimen bank for future work.

Meeting Summary – Day 2

Neuroimaging Working Group Report

Christopher Smyser, M.D., WUSM
Charles Nelson, Ph.D., Harvard University

The Neuroimaging Working Group comprises several modality subgroups: MRI Hardware, MRI Acquisition/Study Design, MRI Analysis, EEG, fNIRS, and magnetoencephalography (MEG). Most sites included MR imaging/expertise as part of Phase I proposals; participation for other modalities varies across sites.

Seeking to leverage innovations in the field, the Working Group defined a framework for how imaging can support a better understanding of typical brain development as well as deleterious effects of drug exposure, early life stress, etc., and elucidate relationships between brain structure and function markers and measures of neurodevelopment.

Surveys were completed across modalities to assess hardware and software capabilities and scientific priorities. Workflow diagrams were prepared across modalities to identify priority topics, domains of interest, primary outcomes, and current gaps or limitations and opportunities. Survey responses informed the development of a list of hardware resources. All sites are using 3T MRI research scanners, which simplifies protocol development and harmonization. The Working Group assessed the current state of the field for innovative acquisition approaches in neonatal/pediatric populations such as compressed sensing, motion correction, and acoustic de-rating. The Working Group further evaluated portable and in-neonatal care unit MRI scanners and developed strategies for harmonizing sequences across the big three scanner vendors.

MRI Acquisition/Study Design deliverables include a catalog of sequences; domains studied; core protocol suggestions with a data-driven goal duration of 40–60 minutes; preliminary study designs, including feasibility and requirements such as sample size and scan order; and a catalog of required/recommended scanning materials across ages. Workgroup members submitted their “ideal Phase II protocol” for children in two age groups (0 to 2 years and 2 to 10 years), and there was a high degree of congruence. Methods for shortening sequences, optimizing quality, and incorporating spectrometry and other sequences were discussed. Most sites have established age-specific desensitization procedures to help children be comfortable in the scanning environment. The Working Group agreed that desensitization procedures should reflect developmental stages rather than chronological age.

Analysis deliverables across modalities include identification of primary outcome measures of interest; generation of a core list of analysis pipelines; identification of key focus areas for successful neonatal data pre-processing; and construction of a data repository to facilitate evaluation of data quality and pipeline implementation. Numerous procedures for data harmonization are available, but optimal procedures remain to be established.

Much of the data generated across the MRI Acquisition/Study Design, Hardware, and Analysis subgroups have been synthesized and combined into a one-page document. There is consensus across core elements of imaging protocol composition, target duration, and periods for increased sampling, and subgroups expressed a strong desire to leverage technical innovation to foster new lines of research. Next steps for MRI include constructing a data repository to foster data sharing; evaluating pipeline compatibility; harmonizing data across scanners and sites; and communicating with vendors to foster compatibility.

Dr. Nelson presented updates on other imaging modalities. An overview of EEG highlighted advantages such as the ability to record electrical activity off of the scalp during resting state as well as during perceptual challenges, millisecond precision in temporal resolution, and ease of use for infants, toddlers, preschoolers, and school-aged children. However, EEG does not offer good spatial resolution, although recent advances in source modeling allow for identification of sources of the electrical activity.

Different EEG hardware systems are used across sites (i.e., Brain Vision, EGI, and Neuroelectrics). Dr. Fox recommended using the Neuroelectrics Enobio system for home visits and Brain Vision's R-Net or EGI for lab visits. The EEG subgroup recommended setting up a system to simultaneously record one channel of EKG/ECG.

Tasks and scheduling of EEG from infancy through childhood include a baseline of 5-minutes duration; mismatch negativity (MMN) of 15–30 minutes in infants and 15–20 minutes in early to late childhood; visual evoked potential (VEP) checkerboard of 5-minutes duration in ages 1–12 months; and the zoo task (go/no-go) starting at age 3 for 25–30 minutes in early childhood and 20 minutes in middle to late childhood. Overall, a battery can be done in less than 45 minutes for infants and 40–55 minutes in childhood (not including capping time). A number of EEG processing pipelines and analysis screens are available that are capable of handling data from different channels, low and high densities, and hardware.

The use of fNIRS offers a number of advantages for the HBCD Study. It can non-invasively assess oxyhemoglobin and deoxyhemoglobin and is useful in hard-to-reach populations. fNIRS can be correlated with fMRI, is less prone to movement artifacts, and is relatively inexpensive. However, some HBCD sites lack fNIRS equipment and expertise, its temporal resolution is poor, and spatial resolution is limited to the cortical surface. Suggested fNIRS assessments in infancy include baseline, a statistical learning task, a social responsiveness task, and a familiar versus unfamiliar faces task; overall, this battery of tests can be completed in 5–10 minutes. Emotion regulation and executive function tasks are recommended for children, with an estimated total time of 10–30 minutes in early and middle to late childhood.

MEG also provides a number of advantages and is well suited for pediatric populations. High-density EEG and MEG have identical temporal resolution. MEG measures are sensitive to developmental changes such as in alpha and gamma rhythms. Because magnetic fields are not affected by the skull, MEG generally provides higher spatial resolution and sensitivity to hemispheric differences that are hard to find with EEG. Homogenizing across sites and MEG machines is easily accomplished. MEG is less affected by fontanels and compensation for movement provides high-quality data for infants and children, and subject preparation time is about 15 minutes.

Discussion

Children are not under the influence of anesthesia at any point in time during any of the imaging described.

Participants commented on the small number of sites that are using fNIRS, possibly due to equipment acquisition costs. Dr. Nelson expressed confidence that if an institution purchased the equipment, people could be trained to obtain high-fidelity data. For example, a highly competent team in Bangladesh collects fNIRS and MRI data and streams them to Harvard for review, processing, and analysis.

A number of studies have shown that MEG effect sizes are larger than one would get for behavioral results. MEG is a rich dataset and can provide a lot of data from 5,000 children rather than 10,000. Dr. Freund asked the Working Group to consider how many sites would need to have the equipment to obtain a reasonable sample size.

Skin color, hair type, and hair color do not present issues for EEG. For fNIRS, thicker hair does require different electrodes, but this is generally not an issue in younger subjects.

There was discussion about the recommended number of MRI scans to conduct in the first year of life. Two scans are preferred, with a strong desire for one scan within the first month of life. The Study Design Working Group will provide recommendations on the best way to stagger and optimize that process. More scans would be better but may not be practical.

The Neuroimaging Working Group recognizes that running MEG systems simultaneously with EEG reduces burden but is not prepared to recommend which other modalities to apply in the same visit. The Working Group must

keep in mind that different modalities are better suited for different ages and for answering specific questions. Families seem interested in the different information each modality acquires.

Grantee Presentations

Motion-Resilient MRI in Early Childhood

Matthew Tisdall, Ph.D., University of Pennsylvania

Dr. Tisdall provided an overview of Phase I aims and the focus on reducing data loss when scanning young children. Phase I aims include developing motion-resilient structural and functional MRI sequences for young children; evaluating feasibility of novel MRI sequences for increasing data quality and reducing data loss; and informing HBCD decisions on neuroimaging timing, sampling strategies, and neurocognitive assessments.

Technical improvements to achieve during Aim 1 include improving the motion-tracking algorithm, optimizing navigator protocols, and optimizing T1 and T2 protocols. To improve the algorithm, new features have been added: automatic finding and tracking the brain; removal of limits on subject motion; and enabling of lower-resolution and faster navigators through registration. The new motion-tracking algorithm is integrated and running in real time. Human testing will begin when COVID-19 restrictions are lifted. Navigator resolution improvements are on hold until testing can begin. For optimization of T1 and T2 protocols, the MRI Hardware subgroup suggested that cross-vendor evaluation of compressed sensing is critical.

For Aim 2, the group is evaluating tradeoffs between two structural scanning techniques. Compressed sensing can accelerate scans, but shorter scanning time means lower signal-to-noise ratio (SNR) and potentially reduces sensitivity to motion. To look at resting-state fMRI with young children, the group is trying to obtain two blocks each with five minutes of data and motion detection. Scanning is terminated after eight minutes or when deemed unlikely to succeed. Improved performance in diffusion-weighted MRI affirms that movie-watching is helpful.

For Aim 3, the group spent four months designing a recruitment approach that targets families living in high-drug-use and high-poverty Philadelphia neighborhoods, communities that are being hit particularly hard by COVID-19. A recent National Public Radio report indicated that drug use in these areas has increased dramatically, in part because the police are not arresting individuals for nonviolent crimes to reduce crowding in jails. Community partnerships have enabled the group to begin enrolling participants in survey research remotely to build rapport with families and to obtain measures of parent-child interaction and stressors associated with COVID-19. Remote measures of child cognition—specifically, persistence and language complexity—are in process. The group is sending links to surveys on SES, adversity exposure, and child and parent health, giving families the option to participate in a 16-day study by text message that includes 5-minute surveys every morning and evening. For 3-year-olds, parents are being asked to take a video of their children brushing their teeth; software tools are being developed to facilitate video coding as quickly as possible so that this approach can be used with a much larger sample. Measures for older children also are being piloted. Parents are asked to video their children answering three questions: What was the best part of your day? What was the hardest part of your day? And, what is something you are looking forward to?

Discussion

There was discussion about age-dependent biases. It is expected that there will be a single set of regularization parameters that works best for any given protocol. Part of the goal for Phase II will be making the parameters consistent or developing a process to harmonize the data across vendors as much as across age ranges.

The IMPACT Study: Imaging Prenatal and Pediatric Populations to Ascertain Childhood Transitions and Tenacity in Children with Opioid Exposure

Xiawei Ou, Ph.D., Arkansas Children's Research Institute; Weili Lin, Ph.D., University of North Carolina at Chapel Hill; Stephanie Merhar, M.D., M.S., Cincinnati Children's Hospital (CCH); Nancy McElwain, Ph.D., University of Illinois; Phillip Brian Smith, M.D., Duke University; Jennifer Vannest, Ph.D., CCH

Dr. Vannest outlined the Consortium's organization, working groups, and Phase I aims. As the Consortium's coordinating center, the Duke Clinical Research Institute has developed IRB protocols across all five sites as well as study manuals, SOPs, and data-sharing agreements.

The Consortium has not only been collecting new fetal, neonatal, and pediatric imaging data but also exploring infant and pediatric neuroimaging data already collected across the sites. Two sites have experience with fetal imaging, which includes structural imaging, placenta mapping, and diffusion tensor imaging (DTI). All have experience imaging neonates, toddlers, and preschoolers, which includes structural imaging and resting-state fMRI.

An imaging study of prenatal opioid exposure effects on brain structure identified differences in subcortical volume and cortical thickness volumes in neonates with prenatal exposures and controls. At 6 months of age, infants with exposures had poorer cognitive scores than controls. Based on these data, the Consortium concluded that fetal imaging is feasible and scalable; infant and pediatric imaging can be performed with high success; and multiple assessments in the first year of life are important to understand complex trajectories of neurodevelopment.

Dr. McElwain summarized cognitive and behavioral assessment activities. These include compiling instruments that tap key domains with high relevance to neural development in three categories: parent and child assessments; parent-child interaction; and child and environment assessments. Considerations for selection of measurements include participant burden, validity and reliability for different ages and longitudinal use, assessment frequency, administration modes (i.e., lab, home, remote), training requirements for administration and/or coding, and types of data captured (e.g., electronic, video, paper) as they relate to privacy issues and data storage.

The battery for a longitudinal study is designed to capture key parent and child assessment domains while minimizing participant burden; for example, the parent report portion takes about 60 minutes to complete. The Consortium advocates complementing the battery with a home visit protocol that captures domains under the family environment, which has a large influence on development. Home visits provide an opportunity for additional assessment of home and neighborhood and administration of the Home Observation for Measurement of the Environment (HOME) instrument. The HOME measures responsivity, acceptance, organization, learning materials, involvement, and variety. The team also developed the Family Maps Inventory (FMI), a semi-structured interview designed for use during home visits with low-income families to assess important aspects of the family and home environment. FMI also supports monitoring for ACE risk.

As a complement to more traditional assessments, the "LittleBeats" wearable device is used to obtain data on acoustic quality of speech, motion, and physiological regulation. The device enables continuous recordings or measurement bursts, multiple analysis levels, and automated assessment using machine learning approaches.

In response to COVID-19 restrictions, the Consortium has IRB approval to assess mother-infant interaction via virtual visits paired with LittleBeats; 22 virtual visits have been completed. Video quality has been good to excellent. Virtually collected data will be compared with data collected in the lab. Even in a non-COVID context, virtual visits capture dynamic interactions between children and their environment and can increase ecological validity.

Dr. Merhar described biosampling activities. Biosamples can be related to neurodevelopment; for example, there is evidence that salivary alpha amylase is related to worse Bayley cognitive and language scores. Biosampling protocols have been developed for collection of toenail and fingernail clippings, urine, and saliva from mothers and collection of umbilical cord tissue from newborns. (Cincinnati's mass spectrometry lab can analyze 44 drugs and metabolites in cord tissue.) Additional biosamples will include buccal swabs from infants and saliva and urine from children.

Consortium sites have substantial experience with recruitment and retention of longitudinal cohorts. Lessons learned from these experiences focus on the importance of building relationships with families. A strong Facebook presence has made a difference, although newer social media platforms need to be considered for HBCD Phase II. There is value in sending information periodically to remind families about the Study and keep them engaged.

Discussion

Structural trajectories should be normalized for head circumference. The opioid exposure group should be matched with the control group (BCP) for SES.

For the developmental curves, BCP subjects were imaged every three months during the first year. The team agreed that it will be critical to have three time points within the first year.

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., NYUSM; Ashok Panigrahy, M.D., University of Pittsburgh Medical Center; Alice Graham, M.S., Ph.D., OHSU

Drs. Graham and Potter presented progress on iOPEN aims. Aim 1 is to develop, implement, and evaluate innovative recruitment and retention strategies for long-term study of pregnant women and their children; aim 2 is to implement a multi-site, standardized, longitudinal MRI and biobehavioral research protocol; and aim 3 is to evaluate MRI data acquisition and processing to maximize data quality.

Recruitment methods considered for potential efficiency and effectiveness include social media, clinics, medical records, and "snowball" (i.e., participant to participant) referrals. EMR support targeted searches by pregnancy status and identified subjects for a rapidly deployed COVID survey.

The group compared the utility of social media across sites and responses to different images based on pilot data; for example, rural sites received more clicks compared with urban sites. Overall, the different recruitment methods enabled rapid enrollment of a large number of pregnant women, mothers of young infants, and partners/fathers. In addition to considering efficiency, considerations for different recruitment strategies should include who they are reaching. Facebook or other social media avenues may be a means for reaching beyond the clinics. For example, compared with women recruited through clinics, women recruited through Facebook were significantly younger, showed greater racial diversity, and had higher rates of self-reported smoking, alcohol use, and SU. Women recruited at clinics had higher rates of reported diagnoses and treatments for mental health disorders as well as for SUDs than did women recruited via Facebook.

Dr. Potter reported on results of a survey designed to identify barriers to participation and better understand the importance of different incentives, visit structure preferences, and comfort with biosample collection. The survey also included questions designed to measure research literacy and MRI knowledge. Differences in beliefs about the right to be fully informed and voluntary nature of research were observed between women who used substances during pregnancy and other groups; this will help inform the consent process. Similar to previous reports, the survey indicated a high level of uncertainty about MRI safety from mothers, fathers and partners. This suggests that additional education about MRI safety is needed.

Survey responses related to research incentives indicated that learning about babies' development is attractive to pregnant women and mothers; pregnant women are also interested in parenting workshops or play group invitations. Some research visit options appealed to most women (i.e., convenient appointments coordinated with doctor visits), ande others differed by group (e.g., home visits). Home visits should be introduced after relationships are established. Most women reported comfort with providing biosamples, although some expressed discomfort providing their babies' blood and their own stool samples. Fathers are more comfortable providing samples from their babies.

The survey also included a question about COVID-19-related stress and disruptions. Results indicate that high worry and greater practical disruption related to the pandemic are seen in pregnant women.

Stakeholders discussed potential benefits of a longitudinal study examining brain development from birth through childhood with an overwhelming response of enthusiasm. Individuals with lived experience perceived this Study as an opportunity to decrease fear and discrimination. Participants viewed the Study as an opportunity for connection with something positive. Having potential to address fear, guilt, and shame among parents who have used substances during pregnancy also was discussed.

Stakeholders identified potential barriers, including prior negative experiences with the medical system and fears about research results. Potential strategies for addressing hurdles include creating relationships, understanding motivations, and conveying awareness of social determinants of health, particularly using a trauma-informed approach. Strategies to other barriers include being mindful of timing of visits and providing multiple transportation options, appointment assistance, childcare, support for MRI-related fear, and meaningful incentives.

Dr. Graham provided progress on Aim 2. MRI protocols were harmonized and sites were visited prior to implementation of COVID restrictions. All of the sites ordered custom-fitted cribs and had them fitted to their scanners, which enables children to fall asleep on the scanner bed.

Remote approaches include refining strategies for low-impact participant data collection at home. Videos and instructions are being developed to guide participants in collecting samples on their own at home.

Dr. Graham also reported progress on Aim 3. The group has monitored motion during functional scans and has existing data showing that real-time motion monitoring improves data acquisition in infants. Framewise Integrated Real-time MRI Monitoring (FIRMM) approximately doubles the amount of usable resting-state data in neonates.

Discussion

There was discussion about the quality of FIRMM data. Evaluation criteria are based on the desired amount of data and the amount of motion deemed acceptable, which vary depending on how the data will be used.

Participants commented on ways to improve research literacy. Some are moving toward more interactive consent presentations to explain study components, which supports going into greater depth with participant questions.

Participants discussed whether differences in movement are associated with exposure. This is an important piece to quantify. Current techniques will enable investigators to see how movement has affected the data and look at movement as a variable of interest.

Maternal, Neurodevelopmental, and Contextual Assessments Working Group Report

Christina Chambers, Ph.D., M.P.H., UCSD
Pat Levitt, Ph.D., CHLA

The Working Group has divided into three subgroups based on domains of expertise: Perinatal, Maternal, and Newborn; Neurodevelopment; and Family and Environment, covering from prenatal through 5 years of age. These

groups have shared current plans and information about ABCD assessments that are relevant to HBCD. Subgroups have chosen key constructs and possible measures. Next steps will include providing recommendations on assessments administration and timing. Guiding principles for the subgroups included:

- Balancing developmental sensitivity with lifespan coherence
- Including direct assessment where necessary for enhancing detection of exposure effects
- Selecting measures that are well suited for brain-behavior linkages
- Selecting measures that represent state-of-the-art methods
- Selecting measures that are socioculturally sensitive
- Including strengths-based assessments.

The Perinatal, Maternal, and Newborn subgroup selected essential measures that would be captured primarily in the context of a prenatal visit. They include mental health; prenatal exposures including medications, illicit drug abuse screening (DAST), nicotine/tobacco, and alcohol; family support; breastfeeding at delivery; maternal sleep quality; mother's medical history and diagnosis; maternal psychiatric diagnoses; obstetric history; prenatal stress; and sociodemographics. Essential newborn measures include child health, NOWS, gestational age and birth size (i.e., birthweight, length, head circumference), and neurobehavior.

The Neurodevelopment subgroup considered domains including social-emotional, cognitive and neurocognitive development, language development, motor and physical development, health and growth (i.e., sleep, physical activity, and nutrition), and developmental psychopathology. The subgroup selected assessments in these domains to be collected at one time point between 3 and 9 months of age, which covered self-regulation, memory and attention, growth and health, and temperament. At about 1 year of age, the subgroup recommended repeating the assessments from the first time point in addition to assessing internalizing and externalizing behaviors, competence, and nutrition. At 24 months, the assessments for the 12-month time point would be repeated in addition to an autism checklist. Annually at ages 3, 4, and 5 years, the group recommended assessments of social competence, emotional regulation, executive function, inhibitory control, growth and health, sleep, temperament, adaptive function, family life, physical activity, screen time, competence, and picture vocabulary or oral reading recognition.

The Family and Environment subgroup selected the following domains of family and environmental risk assessments: individual differences in infant, child, and adult structural and functional brain imaging measures; and associated risk for child psychopathology and later substance use disorders. Risk domains include prenatal SU exposure, prenatal stress, adverse childhood experiences, family history, SES and neighborhood factors, discrimination and health disparities, and nutrition and food insecurity. The subgroup noted that the prenatal assessment provides an opportunity to establish rapport with the mother and assess critical family and environmental factors.

The subgroups recommended that measure selection be balanced with the demands of the larger protocol. A combination of remote and in-person assessment strategies is planned. Relatively frequent remote surveys of key constructs with instantaneous incentives can be used to engage and maintain the sample.

Dr. Wakschlag noted that the principles are useful as a guiding framework, particularly those concerning the balance of pragmatic and developmental sensitivity, linking to ABCD in a coherent way, making use of extant toolboxes and batteries established for ECHO, and taking advantage of cutting-edge developments.

Wrap-Up and Next Steps

Dr. Lauren Wakschlag (NU) commented that developmental consortia are exploring pragmatic opportunities such as computer-adaptive testing for more efficient survey administration and flexibility of modalities, including the

possibility of remote assessments of parent-child interaction. In addition, moving from intensive micro-coding, traditionally used for behavioral measures, to one-pass global coding would reduce coding burden, which is often the biggest impediment.

Dr. Michael Charness (Boston University) remarked on Dr. Volkow's introductory comments on the impact of COVID-19 and, particularly, potential effects on the HBCD Study's ability to focus beyond the developmental profile of neonates to 9-year-olds. Shifting this study to normative brain development and oversampling of people with COVID exposures would lead to oversampling of people with SUDs. While the underlying neurotropic mechanisms of SARS-CoV-2 (the beta-coronavirus that causes COVID-19) have yet to be established, the large number of people who will have had COVID-19 while pregnant highlights the importance of this issue. There are virtually no data available about babies who might have been exposed.

Dr. Charness added that presentations during this meeting suggest that the Study's most important replicable factor is expertise of researchers to execute a research protocol while negotiating community services, law enforcement, and community advocates.

Dr. Terry Jernigan (UCSD) indicated that Phase I investigators have done amazing work to integrate and gather critical information that will be extremely important as a path forward for the HBCD Study Phase II is developed.

Dr. Jernigan further indicated that, although many infants develop into happy and thriving children with strong social, intellectual, and academic growth, a major barrier in identifying causal relationships when the developmental trajectory is skewed is the lack of access to dimensional resources and the scale to estimate plausible sizes and independent effects of causal outcomes. Dr. Susan Weiss (NIDA) indicated that a large, well-characterized cohort is needed to provide data for interrogation in multiple ways. Although data from other ongoing studies can be leveraged to inform HBCD, a study of sufficient size and scope to understand normal variability, identify the factors that could affect resilience, and determine how outcomes can be optimized in various populations is required to advance our scientific understanding.