National Institute on Drug Abuse

HEALthy Brain and Child Development Study

Kickoff Meeting Report

October 17, 2019
Chicago, IL

2-5-2020

Table of Contents

Welcome and Introductions *(Cathy Spong)* 3

Charge to Grantees *(Michelle Freund)* 3

- Background 3
- Study Design 3
- Timeline 4

Ethical and Legal Considerations for the HBCD Study (*John Lantos and Pilar Ossorio)* 4

- Discussion 5

Vision for the HBCD Study *(Nora Volkow)* 7

- Discussion 7

Lessons Learned from the Adolescent Brain Cognitive Development (ABCD) Study and Environmental influences on Child Health Outcomes (ECHO) Program *(Terry Jernigan and Brian Smith)* 8

- Discussion 11

Grantee Presentations 11

- Planning Phase for the Healthy Brain and Child Development Study (HEALthy BCD) in the Los Angeles County Area *(Wei Gao)* 11
  - Discussion 12
- Motion-Resilient MRI in Early Childhood *(Dylan Tisdall and Allyson Mackey)* 12
  - Discussion 13

The Bill & Melinda Gates Foundation Neuroimaging Predictors of Child Health and Development Consortium *(Sean Deoni)* 13

- Discussion 14

Grantee Presentations 15

- HEALthy ORCHARD: Developing Plans for a Baltimore Site of the HEALthy BCD Study *(Daniele Fallin)* 15
  - Discussion 16
- The IMPACT Study: Imaging Prenatal & Pediatric Populations to Ascertain Critical Trends and Tenacity in Children with Opioid Exposure *(Weili Lin)* 16
- Promoting Resilience in Children: Protocol Development for a Birth Cohort Study to Assess Factors Impacting Neurodevelopment *(Doug Dean)* 17
  - Discussion 17
- Biological and Environmental Contributions to Healthy Child Development in a Diverse Population *(Pat Levitt)* 18
  - Discussion 18
- Florida Development in Early Childhood: Adversity and Drug Exposure (FL-DECADE) Study *(Matthew Gurka)* 19
  - Discussion 19
- Investigation of OPioid Exposure and Neurodevelopment (iOPEN) *(Moriah Thomason)* 20
  - Discussion 21

Optimizing Access, Engagement, and Assessment to Elucidate Prenatal Influences on Neurodevelopment: The Brains Begin Before Birth (B^4) Midwest Consortium *(Cynthia Rogers)* 21
The Cumulative Risk of Substance Exposure and Early Life Adversity on Child Health Development and Outcomes *(Amy Elliott)* 22
Discussion 22
Planning for the HEALthy Early Development Study *(Christina Chambers)* 22
HBCD Working Groups *(Michelle Freund)* 23
Discussion 23
Wrap-Up *(Michael Charness)* 25

Welcome and Introductions *(Cathy Spong)*

Cathy Spong, M.D. *(UT Southwestern Medical Center)*, welcomed meeting attendees and noted that the HEALthy Brain and Child Development (HBCD) Study is a much-anticipated and exciting initiative. Dr. Spong thanked grantee participants for their remarkable work in putting together pilot study (Phase I) applications that will inform and help launch Phase II of the HBCD Study.

Meeting attendees introduced themselves by name and institutional affiliation.

Charge to Grantees *(Michelle Freund)*

Michelle Freund, Ph.D. *(National Institute on Drug Abuse [NIDA]),* Director of the HBCD Study, provided a brief overview of NIH expectations and goals for this study, noting that the kickoff meeting represents the launch of its planning phase (Phase I).

Background

The HBCD Study is partially supported by the National Institutes of Health's (NIH's) Helping to End Addiction Long-term Initiative℠ (HEAL Initiative), launched in April 2018.

With an initial investment of $500 million appropriated by Congress in FY2018 and a similar investment in FY2019, The NIH HEAL Initiative℠ is a trans-NIH effort to advance national priorities in addressing the opioid crisis through research on opioid misuse, addiction, and pain. Participating institutes are concentrating on two broad categories of research: one focused on pain therapies and management, and the other focused on opioid misuse, opioid use disorder (OUD) and overdose. The HBCD Study falls into a subcategory of the OUD approach called "Enhanced Outcomes for Affected Newborns," along with the Advancing Clinical Trials in Neonatal Opioid Withdrawal (ACT NOW) longitudinal project. The HBCD Study receives half of its financial support from the NIH HEAL Initiative℠ and half from NIH Institutes, Centers, and Offices interested in development.

Incidence of neonatal abstinence syndrome (NAS) increased by approximately 433 percent between 2004 and 2014. To address this important issue, the HEAL Initiative supports research to generate knowledge and address the needs of infants and children affected by opioid exposure.

Note: OD: Office of the Director
ECHO: Environmental Influences on Child Health Outcomes

Study Design

Key research objectives of the HBCD Study will include characterization of developmental trajectories (e.g., brain, cognitive, behavioral, social, emotional, academic) beginning prenatally and continuing through childhood in a normative population; evaluation of the impact of pre- and postnatal exposure to opioids, opioid treatment medications, and/or other substances (e.g., cannabis, alcohol, tobacco, other prescription or illicit substances, alone or in combination) on developmental trajectories; and delineation of the roles of sex, genetic, epigenetic, social and other environmental factors. Long term outcomes such as risk/resilience in relation to social/behavioral maturation, brain structure and function, and substance use and mental disorders will also be studied. This will be done by establishing a large cohort (~7,500) of pregnant women from regions across the United States significantly impacted by the opioid crisis and following these women and their

children for 10 years. The cohort will include both individuals with opioid (and other drug) exposure and those without.

Focus areas for the planning grants (Phase I) include:

- legal and ethical issues
- recruitment and retention
- neuroimaging, and other assessments of brain function
- other assessment methodologies (behavior, environment, biospecimens, etc.)

The goal of the planning phase is not to arrive at a consensus protocol, but rather to test different approaches to determine the strengths and weaknesses of each. Planning grantees should address the goals described in their applications, while allowing for some flexibility based on workgroup and other discussions with colleagues. HBCD Phase I grantees are expected to generate the knowledge that will lead to a consensus protocol for Phase II. Note that Phase II will be an open competition; thus, funding is not guaranteed or limited to Phase I awardees. To promote equity among applicants, the NIH intends to videocast the subsequent two HBCD PI meetings.

Timeline

Following the kickoff meeting, there will be an HBCD Principal Investigator (PI) meeting in Alexandria, VA, in Spring 2020 (originally planned for April 21-22; revised to May 4-5), and another PI meeting in Fall 2020 (October/November 2020). The funding opportunity announcements for Phase II will need to be released before the planning phase is over in order to make awards in FY21. Progress reports for Phase I grantees are due on August 15, 2020.

Dr. Spong thanked Dr. Freund for the overview and noted that some of the most difficult issues raised during HBCD planning workshops were ethical and legal considerations, to be discussed next by John Lantos, M.D., and Pilar Ossorio, Ph.D., J.D.

Ethical and Legal Considerations for the HBCD Study (*John Lantos and Pilar Ossorio)*

John Lantos, M.D. *(University of Missouri–Kansas City School of Medicine),* provided an overview of four primary ethically controversial topics that are relevant for the HBCD Study:

- research on drugs in pregnant women
- research on neonates and children
- research on use of illegal substances
- research on behaviors that can be considered child abuse

Dr. Lantos acknowledged the probability that the HBCD Study will generate a great deal of media attention and potential controversy emphasizing the importance of a proactive approach as research with pregnant women and children is complex.

Dr. Lantos provided examples of past studies. He began with research on diethylstilbestrol (DES), a synthetic hormone widely used to prevent miscarriage in the 1950s. Several years later DES was found to be a teratogen and carcinogen. Dr. Lantos discussed this particular case to highlight that researchers and the drug manufacturers were held legally accountable even though they had identified lack of efficacy and adverse effects as part of the research study. Dr. Lantos noted that it is likely that this case was a major factor in the current Food and Drug Administration approach to drug approval; leading to strict regulation of research, even more so than clinical prescribing of drugs.

In the case of proposed randomized trials of zidovudine (AZT) to prevent prenatal transmission of HIV, researchers in low- and middle-income countries (LMICs) wanted to randomize participants to doses lower than

those used in the United States, raising controversy over whether enrolling people in these trials was denying them the best available treatment for their condition. In a randomized trial of different target oxygen saturations for premature babies (Surfactant, Positive Pressure, and Oxygenation Randomized Trial [SUPPORT]), results demonstrated that the targets most widely used in clinical practice were not the safest or most effective; however, many thought children were being denied the standard of care.

A lead abatement study done by the Kennedy Krieger Institute (KKI) in the late 1980s and early 1990s examined the effect of differing levels of partial abatement on children in Baltimore. At the time, most homes in Baltimore had lead paint, and Baltimore passed laws requiring the elimination of lead. This process was expensive, and many landlords in the poorest areas walked away from the maintenance of these buildings, leaving individuals and families in dangerous housing. KKI developed a study to determine whether partial and less expensive abatement techniques would be equally effective. During the consent process, participants were informed that their homes would be randomized to receive one of two levels of repairs to reduce exposure to lead paint and dust, and that this approach was to determine how well the different levels of repair worked. Participants were further informed that repairs were not intended or expected to completely eliminate lead exposure and that, as a part of the study, children would be tested for lead; however, follow-up based on the results would not be provided, and parents would need to consult with their regular clinician. After the study concluded, parents sued KKI, claiming that they had not been informed of the risks and that their children were poisoned through negligence. KKI argued that participants had no other chance of living in lead-abated housing, and therefore would have been exposed regardless of study participation. KKI claimed that participation in the study had been beneficial, as all participants received some level of lead abatement that would not otherwise have been possible, and overall levels of lead-paint poisoning decreased in Baltimore by 93 percent as a result of the study.

These examples illustrate some key ethical questions faced when conducting research with children:

- What are the limitations to responsibilities of researchers when they discover a child is at risk?
- If it is discovered in the course of a research study that children are at risk, can the researcher inform and continue to observe, or does the researcher have an obligation to intervene?

Pilar Ossorio, Ph.D., J.D. *(University of Wisconsin–Madison Law School)*, summarized a key legal/ethical question faced by HBCD researchers: What is your obligation to warn people of issues that they would not identify as a danger themselves? Some bioethicists argue that researchers have an obligation to warn people about risks and/or to provide referrals for follow-up. It will be important to build these things into the study design. In the HBCD Study, researchers will consider key issues of referring pregnant women and children for treatment and returning results.

Complex legal issues will also be considered. All 50 states have reporting requirements for children born drug affected. As a part of the planning phase of the HBCD Study, a deep analysis of all 50 states' laws will be performed to look at case law and reporting requirements. An HBCD Ethical and Legal Workgroup will be formed to consider examples of language and strategies used previously, including those that may be needed to work with state and local law enforcement.

Other legal issues pertain to custody law and parental rights. In some states, mothers who have been imprisoned or suspected to be using drugs may lose custodial rights or have parental rights terminated. It will be important to consider how study processes support continued family relationships. There are also considerations specific to conducting research with children who become wards of the state, and it will be critical for HBCD researchers to be aware of what the rules are for each state. The Ethical and Legal Workgroup plans to draft a recommended ethics policy for Phase II, working with all HBCD Phase I teams.

Discussion

Michael Charness, M.D. *(Harvard Medical School, Boston University School of Medicine, VA Boston Healthcare System)*, indicated that the ethical concerns that dominated the planning meetings for the HBCD Study were about balancing risk and benefit for study participants. Dr. Charness asked what

type of benefit would be appropriate to balance that level of risk in an observational study. Dr. Lantos asked whether planning meeting discussions had developed any proposed benefits. Instead of focusing on provision of payment or benefits, he suggested that researchers consider how the study adds to participants' existing level of risk, and whether there are ways to mitigate that. One way might be working with law enforcement and state attorneys general to provide immunity from prosecution to participants.

Lynn Singer, Ph.D. *(Case Western Reserve University)*, indicated that she considers referrals as an opportunity to receive services that would not otherwise be considered and are therefore a benefit to children and families. Dr. Ossorio clarified that some ethicists would view receipt of referral services as a direct benefit of study participation, but others would consider referrals to be important ancillary care, but not a direct benefit. In the HBCD Study, the opioid exposed population may already be at a very high level of legal risk. In some states, both cohabiting parents can lose custody if only one is misusing drugs. The goal is to balance the risk caused by study participation with benefits to the participant and to society. Lisa Parker, Ph.D., has written on this topic and may be helpful as an additional resource.

Dr. Lantos reminded attendees that if a study is designed to identify children who benefit from participation, then the study becomes an intervention study with referrals provided. Dr. Freund asked whether the doctor to whom the child is referred would report risk or harm. Dr. Ossorio responded that this would depend upon the type of finding, as a developmental delay or neuroimaging anomaly would not necessarily require reporting. Without an agreement established for physicians who receive referrals, the study participants would not be protected.

Ashok Panigrahy, M.D. *(University of Pittsburgh)*, noted that non-substance-exposed control participants would also be exposed to risks. Dr. Panigrahy indicated that he believes referring children for services is a direct benefit, but that strong relationships will be needed between researchers and clinical providers. Dr. Panigrahy also stated a concern about working with law enforcement. Dr. Ossorio clarified that researchers need to ensure that law enforcement is a collaborative partner. The HBCD Study will need a policy for assessing whether or not a child is at risk and ensuring that the policy is in place with law enforcement. Dr. Panigrahy noted having a good deal of experience dealing with legal issues and can act as a resource.

Aleksandra Zgierska, M.D., Ph.D. *(University of Wisconsin–Madison)*, stated that as a clinician who treats these populations, she faces the issue of child abuse in her role as a clinician, researcher, or community member. She indicated that the legal issues conflict with the ethical issues on this topic as researchers try to help study participants, not punish. Dr. Zgierska reported that her team had established agreements as a way to provide access to treatment. Dr. Zgierska indicated that she believes study participation provides an extra "safety net" to participants that is a direct benefit.

Dr. Lantos noted that in addiction medicine there is often a contrast between the "right" thing to do ethically and what the law requires. With regards to the design of the HBCD Study, he believes the best approach is to argue for the side of ethics, but plan for legal repercussions. In pediatrics research, many IRBs do not allow research findings or referrals to be considered benefits. Dr. Lantos suggested that proactively outlining risks and benefits and how to address them, would be useful.

Dr. Zgierska noted that provision of resources and referrals is a part of the care for her team. Stephanie Merhar, M.D. *(Cincinnati Children's Hospital)*, indicated that she feels that developing a white paper describing risks, benefits, how they will be addressed, and what standards should be applied to research in vulnerable populations is an excellent idea. This could be a proactive approach to the issue and could garner additional feedback from interested stakeholders. Dr. Merhar reported that Child Protective Services (CPS) in Ohio had offered to give a presentation to her research team delineating research reporting requirements. Dr. Ossorio noted that, although the content would vary from one state to the next, this would be very helpful for the HBCD Study.

Claire Coles, Ph.D. *(Emory University)*, reported that her site has been dealing with the issues of defining benefits and true risks for many years and that sometimes the level of risk is not known. Dr. Coles queried whether there will be a section in the HBCD consent form stating that participants will be asked about abuse and reported in cases where abuse may be occurring.

Amy Elliott, Ph.D. *(Avera Research Institute)*, noted that in South Dakota alcohol use during pregnancy is considered abuse and that South Dakota also arrests pregnant women for this offense. In the week prior to the HBCD kickoff meeting, 52 pregnant women were incarcerated. Dr. Elliott noted that her team has legally established that they are not mandated reporters, with the provision that the research team would supply educational material and referrals to those who needed them.

Dr. Lantos indicated that there is a difference between mandated reporting for alcohol use and mandated reporting for child abuse and that narrow definitions are essential in immunity agreements. Dr. Ossorio pointed out that protecting the mothers from prosecution through immunity agreements may not necessarily be the best thing for the mother or child.

Dr. Spong raised the point that establishing agreements with one authority and then facing succession and the need to establish agreements with the successors will present an additional issue.

Vision for the HBCD Study *(Nora Volkow)*

Nora Volkow, M.D. *(Director, NIDA)*, greeted grantees and offered her vision for the HBCD Study:

The HBCD Study will be one of the most exciting projects in the understanding of how the human brain works, but it will also incur tremendous challenges. Credit is due to the NIDA and NIH team and to the PIs who have committed to these Phase I grants. The Adolescent Brain Cognitive Development (ABCD) Study has empowered researchers to realize that when they come together to address a very important goal, what is extraordinarily difficult can be achieved. The ABCD Study looked to be a very challenging endeavor but has already collected a great deal of data and generated several publications. The HBCD Study will involve research with neonates, which is even more challenging, with a high risk of adverse events; and potentially major legal and ethical hurdles to overcome. Within the HEAL Initiative, the HBCD Study is probably the most ambitious effort, relating not only to the opioid crisis but also to human development. The HBCD Study was developed because, as a Nation, we are facing one of the worst drug crises ever, involving not only the epidemic of prescription and illicit opioid use but also a simultaneous rise in deaths from psychostimulant drugs like cocaine and amphetamines. Understanding what is making the Nation vulnerable to addiction, increased suicide in adolescents and adults, and decreased life expectancy overall, is fundamental. Both environmental factors and genetics are important, but the scientific community does not yet understand how they interact to impact the brain and result in risk and resilience, whether in neurological diseases, physical disorders, or other conditions. The elements of the HBCD Study that target these knowledge gaps are what will ultimately have the largest impact. Program staff are relying on investigators and research teams to make this happen and are available to those that may encounter difficulties. The planning phase is designed to last 18 months in order to establish a sense of potential challenges and how they can be addressed, and to build collaboration among researchers in the field. If, during Phase I, grantees discover that moving forward is not feasible, they should approach NIH program staff and tell them what is needed to continue and succeed. We are now in the era of data science that allows researchers to ask questions that could not be asked in the past, but the quality of the science depends on the quality of the data that are gathered, and quality control is very, very important. Science belongs to everyone, and all can contribute.

Dr. Volkow concluded by reporting that she is very excited about this project, and, while the ABCD Study has been remarkable, the HBCD Study represents a step forward.

Discussion

Dr. Elliott asked what Dr. Volkow would consider to be success at the 18-month time point. Dr. Volkow described success as a demonstration of capabilities: that researchers can work together and with

communities to recruit and retain the populations needed for this studies; that sites have the capacity to perform various types of imaging (e.g., EEG, MRI, others) and provide quantitation of phenotyping; and that all feel responsible for ethics and have "eyes wide open" for the issues they will face as well as plans to address them. Dr. Elliott followed up with a query as to whether these things are what Dr. Volkow believes are needed to launch Phase II. Dr. Volkow indicated that examples of Phase I information that would be evaluated might include the ability of sites to work with child welfare agencies and participants to avoid penalization, the ability to work with dyads of neonates and mothers and provide support to retain them in the study, the imaging protocols that provide the best data including motion artifact correction, and the feasible sample sizes within a specific period of time. All examples represent current uncertainties and data that can be collected during Phase I to create a single protocol for all Phase II sites.

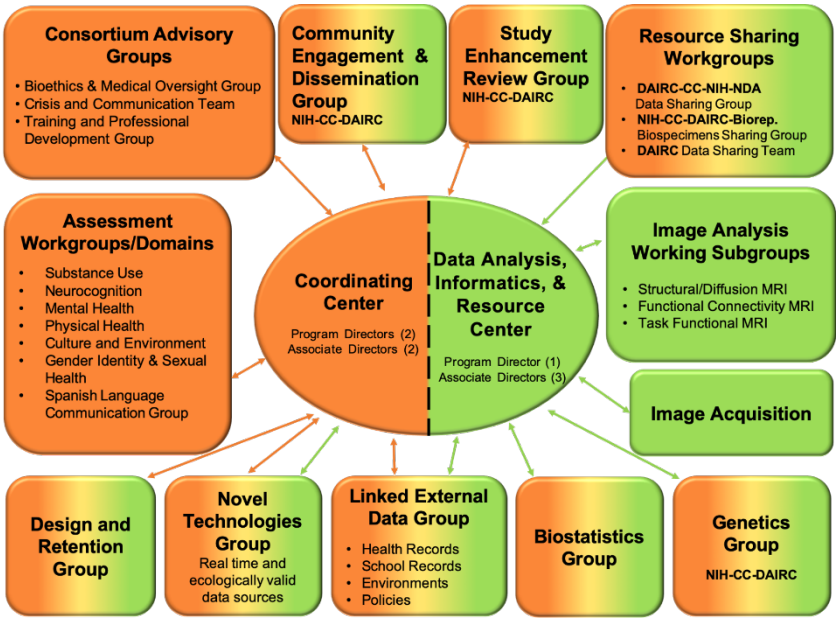
Nathan Fox, Ph.D. *(University of Maryland)*, noted that two studies are apparently being proposed: one of women who use substances or whose fetuses have been exposed to opioids during pregnancy and one defining measures of normative brain development; he asked how Dr. Volkow sees these two components merging. Dr. Volkow indicated that one reason this study presents more complexities than the ABCD Study is that there is an urgency to gather information regarding substances that many neonates are currently being exposed to in the United States. This study will look specifically at opioid exposure, but exposure to cannabis, nicotine vaping, and alcohol are also very high in prevalence. Given that research like the ABCD project is being conducted, failure to try to capture neonatal exposure, alongside normative developmental trajectories for comparison, would represent a missed opportunity. The large cohort will generate a normative data set against which variability in development can be assessed. Deviation from this trajectory may indicate a need for early intervention.

Dr. Lantos asked what Dr. Volkow sees as the top unique ethical problems for questions being asked in the HBCD Study. Dr. Volkow indicated that during the two planning meetings it was made clear to her that the complexity of different regulations in different states regarding women who use drugs during pregnancy and the highly stigmatized nature of using drugs during pregnancy will be critical. Both will present a challenge for enrollment. Additionally, it will be important in the HBCD Study to "go in with eyes wide open to the challenges," including those relating to child welfare and the study of neonates.

Lessons Learned from the Adolescent Brain Cognitive Development (ABCD) Study and Environmental influences on Child Health Outcomes (ECHO) Program *(Terry Jernigan and Brian Smith)*

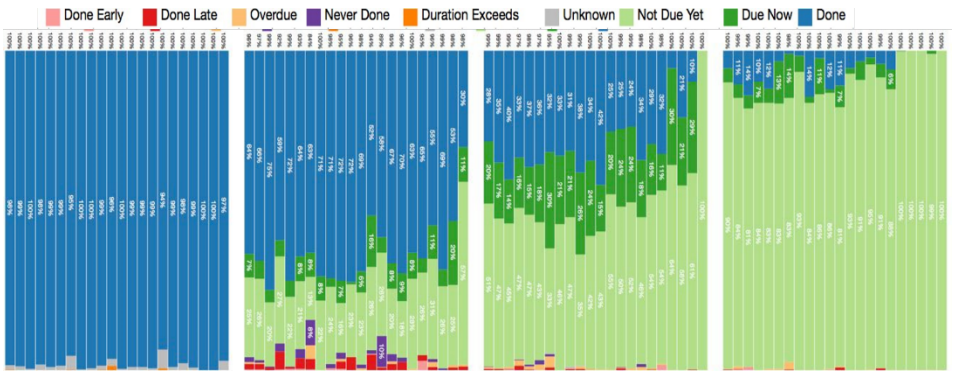
Terry Jernigan, Ph.D. *(University of California, San Diego [UCSD])*, Co-Director of the ABCD Study Coordinating Center (CC), provided an update on the ABCD Study to date. The ABCD Study is a multisite longitudinal study of the developing brain and behavioral functioning. Participants are enrolled at age 9 or 10 and followed through adolescence and young adulthood; the focus is on developmental trajectories and factors influencing these trajectories, especially those pertaining to substance misuse outcomes. The 21 ABCD research sites have recruited participants through school systems, using an epidemiologically informed stratified probability sample of schools selected based on sex, race/ethnicity, socioeconomic status, and urbanicity. A total of 11,880 children were enrolled in the cohort, which approximates the diversity of the U.S. population. The third annual follow-up visits are beginning. The ABCD Data Analysis, Informatics, and Resource Center (DAIRC) has issued two annual curated data releases; the 2019 release includes baseline data as well as early follow-up.

There are approximately 200 ABCD investigators, plus external consultants to fill in gaps in expertise. The consortium relies heavily on experts in workgroups. Proposals and recommendations are brought forward from workgroups to the CC and the DAIRC and then to the operations group for feedback, before being presented to the council of investigators during twice-monthly meetings. Proposals and recommendations are then sent to the steering committee for approval. There are 23 functional workgroups with overlapping subgroups.



To guide the structure of this complex initiative, the National Institute on Drug Abuse (NIDA) has adopted a results-based accountability (RBA) strategy to ensure success. In this transparent model, progress and quality are closely monitored by all consortium members. Dynamic, real-time reporting is used to keep all sites aware of results at all times. This allows constant access to resources and support and enables the ABCD Study to quickly adjust standard operating procedures and adapt trainings to support best practices. The ABCD Study is doing something entirely new, and elements need to be created in real time to deal with challenges as they arise. From the outset, the relationship between NIH partners and the consortium investigators has been very collaborative.

The ABCD Study generates reports that are shared on monthly teleconferences, including continuously updated enrollment tracking and projections at each site as well as across the consortium. This process has allowed the DAIRC to track how well enrollment was meeting targets for race and ethnicity, in both the general population and twin cohorts. Levels of congruence between target population percentages and enrollment have been high, but the ABCD Study extended the enrollment period to bring in more African-American families and increase the enrollment of families with lower education levels. In addition to enrollment, the DAIRC tracks metrics like visit status, generating graphics that illustrate visit scheduling, visit completion, and data quality and completeness.



The ABCD Study is an open science model, partnered with the National Institute of Mental Health (NIMH) Data Archive (NDA). Raw imaging data are available immediately to those with authorization, and accumulated curated data are released annually. Use of data is governed by a data use contract that requires compliance from both internal and external investigators. Terabytes of phenotyping, imaging, genomics, and more are already available to the scientific community.

A number of aspects of the ABCD Study design have worked well. The workgroup structure has been essential, and constant monitoring and RBA have been key in successes thus far. Close interaction with federal

collaborators has been critical. It has also been essential to identify areas for adaptation. The open science model and the data exploration and analysis portal have made complex housekeeping, data coding and analyses possible.

There have also been multiple challenges in ABCD Study. The complexity of the study's design generated motivation to build an infrastructure while beginning study implementation. The HBCD Study will have a slightly gentler slope with the built-in planning phase for design and development. The ABCD Study also faced skepticism from peers who did not believe a study this complex could succeed. Adding new functions, opportunities, elements that require protocol changes, and deploying data quality control have also been challenging. Finally, balancing service needs with scientific engagement has been important; participation in the ABCD consortium is rigorous and demanding, and researchers are participating in exciting science.

Dr. Jernigan closed with advice and recommendations for the HBCD consortium, beginning with centralization of real-time data capture, quality control, and dynamic reporting functions. Dr. Jernigan stressed that this study will define the future of neuroimaging, and that providing support will be particularly important with imaging vendors. Both the ABCD and HBCD Studies will produce complicated large data sets, and the idea is to exploit them. This will be very challenging for the scientific community, but the statistics will be very powerful.

Brian Smith, M.D., M.H.S., M.P.H. *(Duke University)*, presented an overview of lessons learned from the NIH Environmental Influences on Child Health Outcomes (ECHO) program. ECHO is a 7-year initiative capitalizing on existing cohorts to examine the effects of environmental exposures on child health and development. The overall program objectives are to conduct observational and intervention research that will inform programs, policies, and objectives and to institute best practices for the conduct of team science. There are 62 ECHO awards and 71 existing dyad cohorts, as well as a nested Institutional Development Award (IDeA) States Pediatric Clinical Trials Network with its own CC. Cohorts are followed longitudinally, and the ECHO goal is to have cohorts totaling more than 50,000 children.

ECHO utilizes a broad definition of environmental exposures that includes physical, chemical, societal, medical, psychosocial, behavioral, and biological influences. Health outcomes are focused on several key pre-, peri- and postnatal areas such as upper and lower airway health, obesity, and neurodevelopment. There is tremendous heterogeneity among cohorts, as enrollment began years ago. ECHO's goal is harmonized data collection.

To accomplish this, the ECHO study team established a large number of working groups, task forces, and subcommittees. In addition to collaborating to develop the ECHO-wide cohort protocol, these groups provide expertise for publications and presentations, data-sharing and biospecimen policies. Establishing these groups enabled a unified pathway for the communication of information to participating sites and created a forum for ECHO members to share beyond steering committee participation.

Assigning groups to write policy and identify scientific questions helped to define early expectations. Following kickoff, things that worked well in ECHO included assigning CC staff to support each working group and assigning CC faculty to each group for the first year. Dr. Smith noted that, retrospectively, having established short- and long-term goals for workgroups prior to kickoff, instituting formal mechanisms for workgroup participation and length of member commitment, and holding groups accountable would have been helpful.

Dr. Smith also reported that timelines have been critical to ECHO, as well as getting "buy-in" from all stakeholders and NIH support of the timeline. He recommended that the HBCD Study keep the timeline flexible. Task-specific timelines in various formats can be helpful and should be part of the protocol writing.

The site activation process for ECHO is complex with 31 cohort awards and 71 cohorts. The most significant lesson has been the need for deadlines and reporting structures at site, consortium, and federal levels. The informed consent process was also challenging, as the existing cohorts were using different forms. ECHO allows the central IRB model but does not require it. In the local IRB model, ECHO participant sites took the final ECHO consent template and added it into existing consent forms for approval. Development of the ECHO informed consent form template engaged many stakeholders.

ECHO holds monthly steering committee meetings. An advisory committee is made up of representatives from all components of the study who develop goals and an agenda for the meeting. The ECHO CC has found that balance between operational agenda items and the presentation of science is especially important. Working in small breakout groups can be more productive than general session presentation alone.

The protocol development working group was critical. After the protocol was created, the group continued the process of making sure that the protocol is responsive to everyone's needs. The CC collects feedback after every meeting. All ongoing feedback processes have been critical to continued improvement and progress.

Discussion

Dr. Ossorio asked if ECHO and/or the ABCD Study has a process in place for resolving disputes between investigators. Dr. Smith indicated that typically when issues arise that fall outside of established policies, ECHO has an executive committee to address disputes; if needed, problems are escalated to the steering committee, then to the NIH. Dr. Jernigan reported that in the ABCD Study, disputes are brought to the CC, and the steering committee and an external scientific board for added objectivity can be involved, according to the established set of procedures.

Dr. Volkow asked how ECHO can generate data that enable the project team to integrate information, given the heterogeneity of the ECHO cohorts. Dr. Smith noted that the Johns Hopkins analysis center is responsible for compilation and integration. This process has started and is ongoing.

Moriah Thomason, Ph.D. *(New York University)*, raised the issue of potentially identifiable data and asked what approaches are being taken for more complex aspects of data sharing. Dr. Smith reported that all data sharing is governed by the ECHO data-sharing policy. The policy dictates that anyone can access data, but if the data involve personally identifiable information (PII), then all analyses must be conducted by the ECHO data analysis center. Dr. Thomason asked what will happen when the ECHO project ends. Sean Deoni, Ph.D. *(Brown University)*, clarified that in ECHO, no data are downloadable; all data exist in a cloud-based sandbox. Non-PII data can be analyzed in this system by the accessing researcher, but PII data can be analyzed only by the data analysis center. Dr. Deoni agreed that the project wrap-up for ECHO is going to be a challenge and a lesson in these matters.

M. Daniele Fallin, Ph.D. *(Johns Hopkins University [JHU])*, pointed out that the design of ECHO provided 2 years for a "ramp-up" phase. Dr. Deoni indicated that the purpose of the planning phase in the HBCD Study differs from the purpose of the planning phase in ECHO. In ECHO, the planning phase was designed to determine whether or not it would be possible to bring participants back and to establish a common protocol. This differs from the HBCD Study, where the purpose is to determine feasibility.

Dr. Elliott stated that having 1,200 individual investigators has been a challenge in ECHO. ECHO investigators were initially funded for individual proposals, and there is a question of how to continue this work and participate in a consortium. Dr. Volkow noted that, for HBCD, it would be premature to combine data until it is clear what data look like, how data are organized, and how the workgroups function.

Grantee Presentations

During this session, HBCD planning grant awardees were asked to present brief overviews of their Phase I projects.

Planning Phase for the Healthy Brain and Child Development Study (HEALthy BCD) in the Los Angeles County Area *(Wei Gao)*

The HEALthy BCD in the Los Angeles County Area project includes a team of four PIs. Imaging specialist Wei Gao, Ph.D. *(Cedars Sinai Medical Center)*, introduced the other three PIs by area of specialty: Kim Gregory, M.D., Obstetrics/Gynecology *(Cedars Sinai Medical Center)*; Charles Simmons, M.D., Neonatology *(Cedars Sinai Medical Center)*; and Ken Bachrach, Ph.D., Substance Use Disorder Clinical Research Director *(Tarzana*

Treatment Centers). Additional team members and external consultants include imagers, developmental psychologists, a gastroenterologist and radiologist, and statisticians from the University of California, Los Angeles (UCLA), Cedars Sinai, and the University of North Carolina at Chapel Hill (UNC).

Planning phase goals for the Los Angeles County Area project are to recruit 10 mother-child dyads with prenatal opioid exposure, 10 with prenatal exposure to other drugs, and 10 drug-free control dyads. Mothers will be recruited for the study during the second trimester of pregnancy, and mothers and children will be followed until children are 6 months of age, with imaging and developmental assessments at 3 weeks and 6 months of age. In addition, five babies with postnatal opioid exposure from the Neonatal Intensive Care Unit will be followed and assessed along with those with prenatal exposure for comparison, and ten 1-year-olds, five 3-year-olds, and five 6-year-olds with postnatal opioid exposure will also be included.

The project is set in Los Angeles County, where there is a racially, ethnically, and socioeconomically diverse population. Although Cedars Sinai Medical Center and UCLA are in affluent communities, Tarzana, Long Beach, Lancaster, and Riverside are less affluent, and participants will be recruited from all six areas.

Working with Dr. Grewen, the team has nearly completed two projects using neuroimaging to examine the effects of prenatal drug exposures. Data sets include 45 babies with prenatal cocaine exposure, 43 with other drug exposure, and 64 control subjects. The team has also published several papers on the effect of drug exposure on neonatal brain functioning.[1-3]

In collaboration with Dr. Li at the Research Institute at Cedars Sinai Medical Center, the team plans to pilot a multitasking sequence of whole-brain simultaneous T1/T2 mapping to reduce acquisition time and resolve motion in imaging. They are working with Dr. Johnson at UCLA on standard and novel tests of cognitive and socioemotional development during infancy.

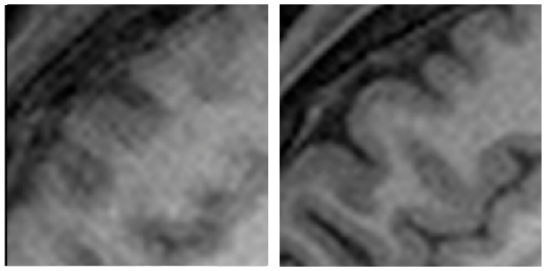
Discussion

Dr. Spong queried whether this project would conduct fetal or infant imaging. Dr. Gao indicated that this study performs only postnatal imaging.

Motion-Resilient MRI in Early Childhood *(Dylan Tisdall and Allyson Mackey)*

Dylan Tisdall, Ph.D. *(University of Pennsylvania [Penn])*, and Allyson Mackey, Ph.D. *(Penn)*, provided an overview of the methodology proposed by the Penn team to evaluate the feasibility of novel technologies for minimizing motion-induced bias in imaging of young children. The team has worked with numerous methods of training 4-year-old children to remain still during neuroimaging, but motion remains a challenge. Children with Attention-Deficit Hyperactivity Disorder and lower socioeconomic backgrounds tend to move more than others, and it is important not to exclude these children from the HBCD study samples.

The lab is working to develop motion-resilient imaging and tools to generate improved sequences for image quality when motion has occurred. The Penn research team will also include optimization of imaging for lighter myelination and smaller head size in children. Novel three-dimensional (3D) sequences will show video of parent-child interactions during structural and non-resting-state fMRI, and the protocol will be tested in 100 3- to 5-year-old children recruited from an area in Kensington, Philadelphia with



No motion correction vNav motion correction

[1] Salzwedel AP, Grewen KM, Vachet C, Gerig G, Lin W, Gao W. Prenatal drug exposure affects neonatal brain functional connectivity. *J Neurosci.* 2015;35(14):5860-5869.
[2] Salzwedel AP, Grewen KM, Goldman BD, Gao W. Thalamocortical functional connectivity and behavioral disruptions in neonates with prenatal cocaine exposure. *Neurotoxical Teratol*. 2016 Jul-Aug;56:16-25.
[3] Grewen K, Salzwedel AP, Gao W. Functional connectivity disruption in neonates with prenatal marijuana exposure. *Front Hum Neurosci.* 2015;9:601.

high rates of poverty and drug use. Penn partnered with Brightside Academy and Brian Work, M.D., M.P.H. to address recruitment challenges.

The Penn team will collect environmental measures and assessments of cognitive and affective development. In combination with imaging, this information will be used to identify predictors of increased likelihood of movement during imaging in preschool-aged children and inform sampling strategies for future studies.

Discussion

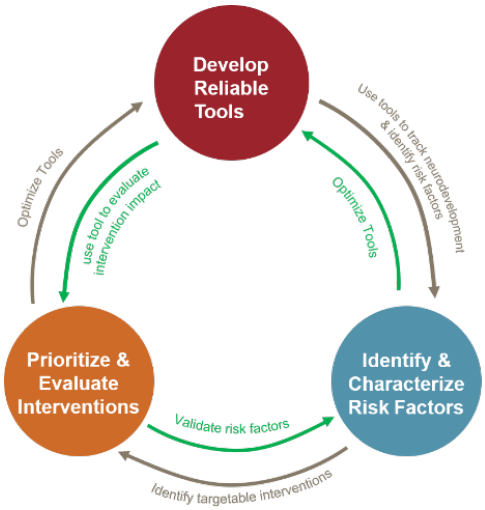
Dr. Lin reported that, as a part of the Los Angeles HEALthy BCD study, the imaging team is using video with children during the scan, but that with children older than 3 there are issues with how to analyze functional connectivity. Dr. Tisdall indicated that he would like to find a way to bring participants back for additional visits to attempt to address that issue.

Dr. Volkow noted that Kensington represents one of the most deprived and difficult environments. With repeated relapse and low treatment success, it will be difficult to retain study participants. Dr. Tisdall noted that past studies have recruited from these neighborhoods but not from clinics, and this is one reason the Penn team has included Dr. Work. The Penn team is less concerned with retention at this stage than with whether the measures are feasible. Dr. Volkow indicated that modeling the feasibility of retention is also an important factor in Phase I of the HBCD Study. Dr. Tisdall noted that bringing participants back for follow-up will help to illustrate factors of recruitment and retention.

Dr. Lantos asked if there are any benefits to participation in the Penn study. Dr. Mackey indicated that the Penn group has collated resources to provide for participants, and social work students will help with recruitment and retention. Dr. Lantos pointed out that individuals could receive resources without participating in the MRI. Dr. Mackey indicated that the Penn team allows individuals to participate and refuse MRI, but in past studies that children enjoyed the attention and seeing pictures of their brain. Dr. Lantos suggested that follow-up on children's perception of the experience could be informative. Dr. Lin noted that her team has had similar positive experiences with repeated imaging of children. Dr. Thomason reported that she has also had children draw themselves in the MRI machine after scans.

The Bill & Melinda Gates Foundation Neuroimaging Predictors of Child Health and Development Consortium *(Sean Deoni)*

Sean Deoni, Ph.D. *(Bill & Melinda Gates Foundation [BMGF])*, presented the work of the Neuroimaging Predictors of Child Health and Development (NPCD) Consortium. Past studies by Charles A. Nelson III, Ph.D., and Dr. Deoni's team have indicated that children in adverse conditions or in low parental education groups show differences in cognitive functioning by age 2. An estimated 250 million children under 5 fail to meet their developmental potential.

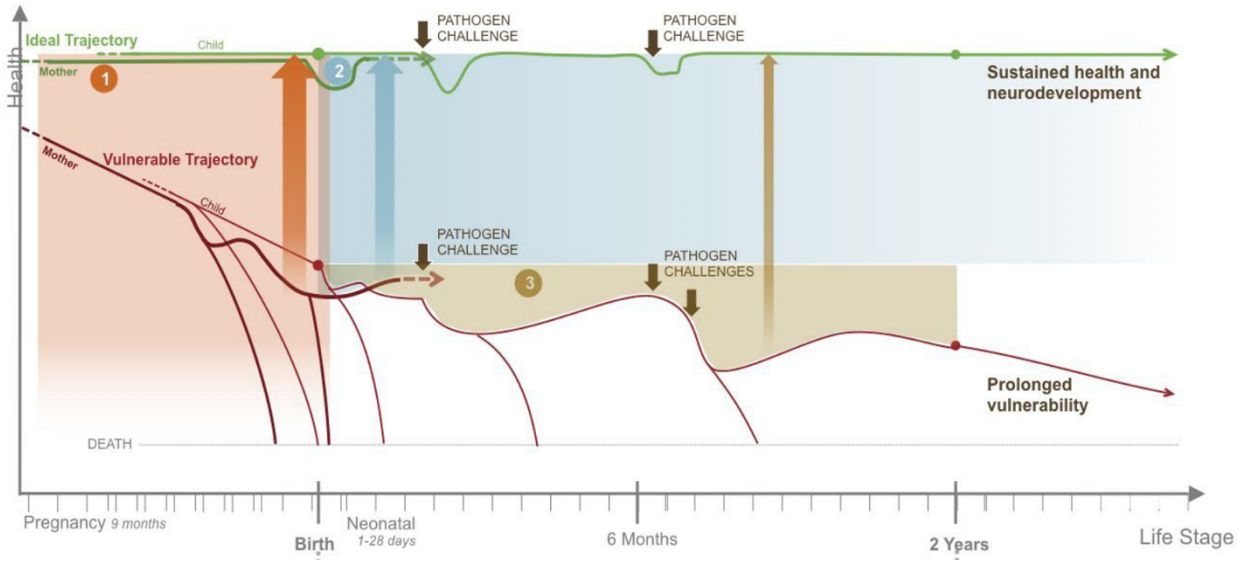


There are no globally standardized objective tools to accurately assess a child's developmental trajectory. Without the ability to accurately assess developmental status and potential, it is not possible to identify risk. These data are necessary to characterize interventions. The overall objective of the neurodevelopmental consortium is to identify children on a vulnerable trajectory and bring them to an ideal trajectory.

The project is focusing on the postnatal portion of the first 1,000 days. Neuroimaging of cortical development may offer more predictive tools than behavioral assessments. Imaging allows direct measurement of biological processes that are known to change across the first 1,000 days, potentially providing more insight into neurodevelopment than classic cognitive measures during this time period.

The consortium intends to achieve its goals by bringing together experts and resources. Members include several external data contributors from the University of Minnesota, Twin Cities, and the University College London, data analysts from the University of Rochester, the University of California, Berkeley, Princeton University and the University of Chicago, and additional internal data scientists. The BMGF NPCD Consortium intends to relate pre- and postnatal environmental exposures to brain structure and function, and to relate both exposures and imaging data to cognitive and developmental outcomes.

Addressing vulnerability to survive and maximize growth and neurodevelopmental potential



To date, data have been gathered in physically stunted and non-stunted children, including gray and white matter volume information, EEG and resting-state MRI brain connectivity data, and myelination. Standardization of data can be done through a data integration model. Because standardized acquisition and analysis were not options for the BMGF NPCD, the consortium utilized a data harmonization approach. This maintains consistent naming conventions, metrics, outputs, formats, and organization.

The BMGF Brain Imaging Data Structure Format includes extensions to allow longitudinal data analysis, as well as new functional near-infrared spectroscopy (fNIRS) standards based on EEG data. The team has constructed LMIC-specific whole-head and brain tissue templates from 180 children from India. Age-specific masks aligned to Montreal Neurological Institute (MNI) space have been created for 3, 6, 9, 12, 15, 21, 24, and 30 months of age. Traveling human phantoms were used to assess mapping between sites. The consortium hopes to identify additional mapping factors related to differences in diet and other environmental factors.

The consortium is finding ways to identify the shortest possible sequence for a high-quality functional connectivity matrix, using data harmonization and traveling volunteers. Next steps involve a stepwise analysis plan to characterize brain development patterns predictive of executive functioning and academic performance; identify relevant pre- and postnatal environmental exposures that affect brain development and cognitive outcomes; identify developmentally sensitive periods when children are at risk; and determine when to perform imaging and data collection. Additional objectives include characterizing the stability and reproducibility of each measure and striving for the most scalable versions for study geographies.

There is strong alignment between the goals and aims of the BMGF Consortium and the aims of the HBCD Study. Both will demonstrate that difficult studies in challenging locations with sensitive populations are possible and feasible. Advancements in technology, including everyday bedside MRI, may be game-changing.

Discussion

Pat Levitt, Ph.D. *(Children's Hospital Los Angeles)*, questioned the goal of arriving at a single measure because no one measure is ideal in all situations. Dr. Levitt also asked how the BMGF NPCD is dealing

with heterogeneity in imaging. Dr. Deoni indicated that the study results will not generate a single measure but a collection of measures, including MRI, cognitive, diagnostic, and demographic information. Dr. Deoni also noted that heterogeneity is a factor in all development, what is important is not only deviation from the group but also an individual's deviation from his or her own mean.

Dr. Volkow noted that because BMGF is restricted to a smaller developmental time window, interventions will not indicate whether or not deviation is abnormal long term. Dr. Deoni noted that BMGF is collecting longitudinal data but is looking at the window before age 2 because there is a lack of existing accurate predictive measures during this period. Dr. Volkow asked whether mental illness is also considered. Dr. Deoni indicated that it was necessary to limit to academic achievement.

Lauren Wakschlag, Ph.D. *(Northwestern University)* commented that investigators should be careful not to discard the Bayley and the Mullen Scales of Early Learning (MSEL). Dr. Deoni indicated that in addition to using the Bayley and MSEL, the BMGF NPCD Consortium is using the Global Scale for Early Development (GSED), a composite developed with the World Health Organization that has been translated across languages for international use.

Grantee Presentations

HEALthy ORCHARD: Developing Plans for a Baltimore Site of the HEALthy BCD Study *(Daniele Fallin)*

M. Daniele Fallin, Ph.D. *(JHU)*, introduced the HEALthy ORCHARD (Origins of Child Health And Resilience in Development) project. Dr. Fallin introduced the project team, including members of the Ethical and Legal team, Neuroimaging team, Data Science and Methods team, and Recruitment, Retention, Community and Data collection team.

HEALthy ORCHARD is using the infrastructure of an existing birth cohort of the ORCHARD study at JHU. The team brings together colleagues in the JHU area, including the JHU Berman Institute of Bioethics, to address ethical and legal challenges. The study also includes individuals responsible for starting the national Special Supplemental Nutrition Program for Women, Infants, and Children program; the JHU Bloomberg School of Public Health; and the data analysis team for the ECHO study.

Aim 4: Data Collection Planning

		Prenatal			Perinatal/ Infancy			Early childhood			Middle childhood
		T1	T2	T3	Birth	Neo nate	6 mo	12 mo	18 mo	Yearly 2-4yr	Yearly 5-10yr
Mother											
Substance use											
Psychosocial	Social*										
	Employment/Education										
	Housing										
	Poverty										
	Violence										
	Stress										
	Parenting										
Medical/Health	General										
	Obstetric history										
	Behavioral										
	Psychiatric										
	Care access										
Environmental	Toxicants										
	Nutritional										
	Physical activity										
	Community										
Biomarkers	Genetic/Epigenetic										
Child											
Psychosocial	Social										
	Cognitive										
	Behavioral										
	Stress/Trauma										
Academic											
Medical/Health	General Health										
	Neonatal Health										
	Psychiatric Diagnoses										
	Behavioral Diagnoses										
Biomarkers	Neuroimaging										
	Eye Tracking										
	Genetic/Epigenomic										
Environment	Toxicants										
	Nutrition										
	Physical Activity										
	Community										

In developing the HEALthy ORCHARD study, the team structured aims around multisite protocols for recruitment and retention, establishing community, medical, and government partnerships, addressing ethical and legal challenges, and conducting longitudinal data collection across pregnancy and childhood on social, environmental, and genomic factors influencing brain development and outcomes at age 10.

The team organized workgroups around each aim and sub-aim. Providing benefits and support is considered a part of the legal and ethical challenges when working with substance-using women. Biosampling and other assessments evolve over time; the team proposes workgroups for basic protocols and longitudinal outcomes.

The HEALthy ORCHARD created an example grid for potential data collection points. The grid includes examples of the types of information the study team hopes to harmonize and standardize from substance-using populations. The HEALthy ORCHARD workgroups have been working to map assessments to longitudinal outcomes in Research Domain Criteria domains and other classification systems.

From participation in the ECHO study, the team has learned to think about early wins and concrete deliverables, encourage common protocol development, develop clear timelines, and respect multiple areas of expertise.

Discussion

Dr. Spong asked if imaging will be postnatal. Dr. Fallin indicated that it would be and that the plan is to perform imaging at 6 months of age.

Dr. Volkow requested clarification of the recruitment plan in the current protocol. Dr. Fallin noted that the ORCHARD study currently recruits 100 women per year, and 10-15 percent use opioids. Dr. Volkow reminded attendees that the HBCD Study plans to recruit 15 percent of women exposed to opioids and 85 percent non-opioid-using women.

The IMPACT Study: Imaging Prenatal & Pediatric Populations to Ascertain Critical Trends and Tenacity in Children with Opioid Exposure *(Weili Lin)*

Weili Lin, Ph.D. *(UNC)*, introduced the five institutions participating in the Imaging Prenatal & Pediatric Populations to Ascertain Critical Trends (IMPACT) study: UNC, Cincinnati Children's Hospital, Duke Clinical Research Institute (Duke CRI), Arkansas Children's Research Institute, and the University of Illinois at Urbana-Champaign. The study is designed to address three aims: 1) develop instruments and strategies that may be used in the HBCD Phase II study; (2) conduct pilot studies to evaluate those instruments; and (3) to analyze available data, including imaging, behavioral, cognitive, and maternal data from studies focusing on early brain development. Many team members are conducting ongoing studies with neuroimaging data. This Phase I project will determine whether the IMPACT team can develop an approach for data harmonization.

The IMPACT project model is based on the infrastructure of the ABCD Study and includes a CC, an Image and Data Analysis group, four study evaluation sites, and a site focused on developing and piloting a smart shirt device. The team is leveraging the CC at Duke CRI to manage consortium IRBs as well as study management and documentation. The project is also leveraging imaging analysis expertise at UNC to develop pediatric neuroimaging tools. With four sites collecting imaging data, all three main magnet vendors are represented (Siemens, Phillips, and General Electric), and the IMPACT group plans to scan approximately 20 subjects at Duke CRI and UNC to compare with General Electric and Siemens scans.

Study 1 of the IMPACT project will recruit 45 women in the second trimester of pregnancy, perform imaging during the third trimester, and collect maternal and delivery biological samples. The 45 children of these women will be retained, and 75 additional children aged 0-5 years will be recruited to participate in Study 2. This postnatal phase will include maternal factor reporting, biological sampling, and imaging to practice data collection. Study 3 will look at data on the influence of opioids on the neurodevelopment trajectory using neuroimaging data collected in previous studies, harmonizing data collected on different scanners. Study 4 will utilize a smart shirt worn by participants to allow data acquisition in the home.

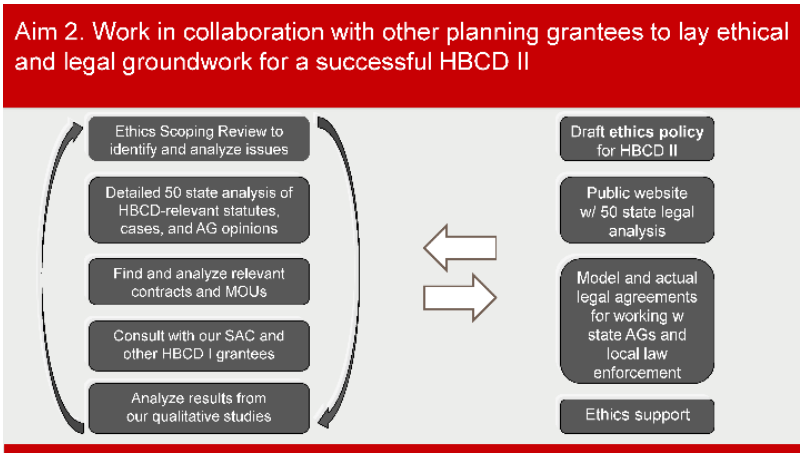
The team continues to develop imaging tools, including fetal brain extraction,[4] but data collection is only one component. Analysis tools are also necessary, and methodology developed by the IMPACT team achieved the highest percentage of usable data. The IMPACT project team is also looking at data harmonization using a Surface-to-Surface CycleGan approach to harmonize data from two cohorts (UNC/University of Minnesota Baby

[4] Lou J, Li D, Duc Bui T, et al. Automatic fetal brain extraction using multi-stage u-net with deep supervision. In: Suk HI, Liu M, Yan P, Lian C, eds. *Machine Learning in Medical Imaging*. MLMI 2019. Springer, Cham; 2019:592-600. *Lecture Notes in Computer Science*; vol 11861.

Connectome Project Consortium) with different protocols and scanners.[5] The team is working with P. Ellen Grant, M.D. *(Boston Children's Hospital)*, to refine the fetal imaging protocol and implement this protocol in pediatric scans on three scanners. Finally, the smart shirt provides measurement of motion and distance, and it pairs with a wristband worn by a parent to provide data on parent-child interaction and physical parameters.

Promoting Resilience in Children: Protocol Development for a Birth Cohort Study to Assess Factors Impacting Neurodevelopment *(Doug Dean)*

Doug Dean, Ph.D. *(University of Wisconsin–Madison)*, presented the three-pronged approach of the University of Wisconsin–Madison HBCD Phase I project. Aim 1 is to develop recruitment and retention protocols for a birth cohort study that supports oversampling for opioid-exposed births. The primary focus is to establish a wide variety of different focus groups and develop in-depth interviews with some of the opioid-using women. As previously described by Dr. Ossorio, Aim 2 is to address ethical and legal issues. The team will provide a scoping review to identify and analyze issues and offer options and solutions that are ethically permissible. This will involve a detailed analysis of relevant statutes in all 50 states as well as cases, state attorneys general opinions, and consultation with other grantees.



Aim 3 of the project involves developing and pilot-testing age-appropriate protocols for pediatric neuroimaging, neurocognitive assessment, and collection of biological specimens. The University of Wisconsin–Madison team has extensive experience with scanning challenging pediatric populations and has developed techniques to correct for motion and construct multiple different contrasts in an 8-minute scan. Although the sequence has not yet been tested in early infant populations, the team believes optimizing the sequence is feasible. The Wisconsin group has experience with microstructural imaging in pediatrics, including diffusion imaging and relaxometry. In addition, the group plans to translate functional tasks and develop an fNIRS protocol to pilot in 10 infants and children. Once finalized, the protocols will be tested in a larger population of 60 participants, from 0- to age 10-years.

Discussion

Dr. Lantos reported that he has been doing exploratory genome sequencing in newborns. He asked what investigators will tell parents when they find a gene variant of uncertain significance. Dr. Volkow pointed out that this is an issue the ABCD consortium has been dealing with. Dr. Jernigan reported that the ABCD Study has already scanned 11,000 children and has seen a lot of anomalies. The ABCD Study has established four categories: no anomalies, anomalies not known to have clinical significance, and two degrees of urgency of addressing anomalies (routine follow-up versus immediate follow-up). Anomalies of no known clinical significance are left to PIs to handle, and each site has an individual responsible for responding to MRI findings.

A question was raised regarding the 50-state survey—how will the team connect to state attorneys general and law enforcement, and how will the team deal with succession and problems that arise?

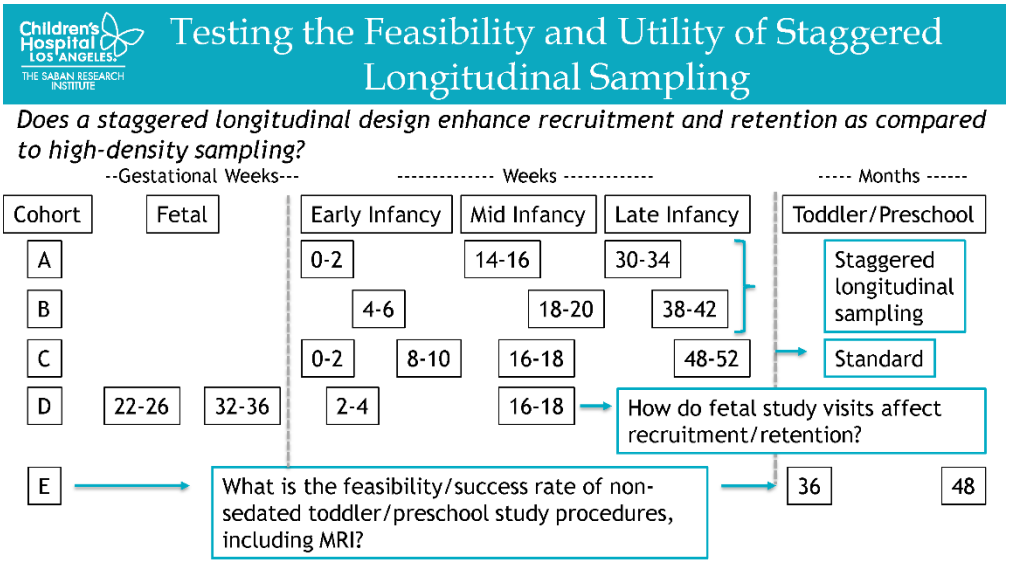
[5] Zhao F, Wu Z, Wang L, et al. Harmonization of infant cortical thickness using surface-to-surface cycle-consistent adversarial networks. In: Shen D, Liu T, Peters TM, et al., eds. *Medical Image Computing and Computer Assisted Intervention*. MICCAI 2019. Springer, Cham; 2019:475-483. *Lecture Notes in Computer Science*; vol 11767.

Dr. Ossorio reported that the legal and ethical team plans to survey different laws to understand what agreements have been reached in states with different statutes and cultural attitudes.

Biological and Environmental Contributions to Healthy Child Development in a Diverse Population *(Pat Levitt)*

Pat Levitt, Ph.D. *(University of Southern California),* provided an overview of the Children's Hospital Los Angeles (CHLA)/University of Southern California HBCD Phase I project. The project has three aims: 1) develop strategies to recruit and retain a diverse sample of pregnant women, 2) develop strategies for managing potential legal and ethical challenges and ensure access to support services, and 3) determine a potential optimal study protocol for the planned Phase II study, balancing longitudinal data collection with minimizing burden on the mother-child dyads.

Los Angeles County is racially, ethnically, and geographically diverse. CHLA has a strong relationship with a community organization that works with families with various issues. CHLA is in an area with high rates of adverse childhood experiences, approximately 18,000 annual births, and three perinatal addiction centers. The CHLA group plans to test a staggered longitudinal sampling method to recruit five cohorts of mother-child dyads (see graphic). With this study design, CHLA will evaluate the impact of staggered sampling on recruitment and retention. The study team will use the preschool-aged cohort to assess the feasibility of non-sedated study procedures, including imaging.



In addition to imaging, the CHLA group will collect questionnaires about maternal status, health and well-being, and family stress. Video and audio recordings will be used to evaluate mother-child interactions. CHLA will collect eye-tracking data using the EyeLink® system and Electrical Geodesics, Inc., with 128-sensor EEG and devices that record motor behavior. These devices are placed in the infant's socks and record for up to 48 hours. Biosamples will include buccal and cheek swabs, blood-spot analysis metabolomics and exposomics.

The CHLA HBCD team will work with the Innovation Studio to adapt a mobile application to provide tools and information for parents bringing premature infants home from the hospital. The CHLA site is also working with Alexander Capron, L.L.B., M.A. *(University of Southern California Gould School of Law)*, to develop workshops to delve into ethical training and logistics for conducting this study.

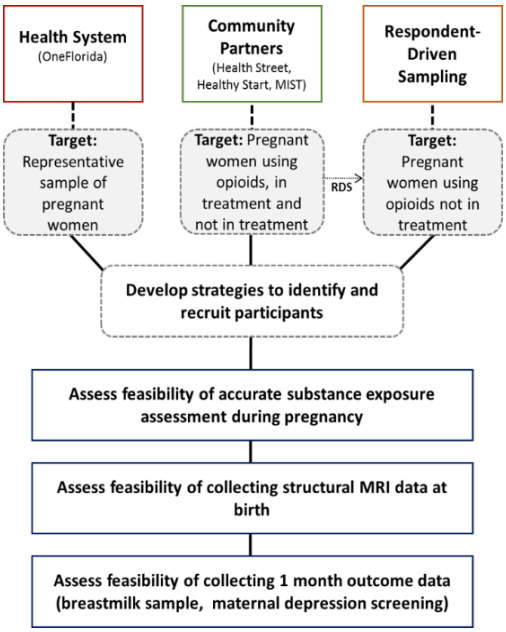
Discussion

Dr. Volkow asked whether the video recording of mother-child interaction is standardized. Dr. Levitt indicated that mothers and children engage in 2 minutes of free play, 2 minutes of mother non-responsiveness, and 2 minutes of engagement. Video is recorded during this 6-minute period.

Florida Development in Early Childhood: Adversity and Drug Exposure (FL-DECADE) Study *(Matthew Gurka)*

Matthew Gurka, Ph.D. *(University of Florida [UF])*, described the FL-DECADE HBCD Phase I study to determine the feasibility of recruitment of normal and high-risk pregnant women and their children across the state of Florida. Dr. Gurka introduced the multidisciplinary study team, including core clinical researchers, an epidemiological methods team, and current UF partners, as well as HealthStreet, UF Anita Zucker Center for Excellence in Early Childhood Studies, UF Levin College of Law, Meridian, Florida Healthy Start, the ABCD team, the UF Health study team, the UF Family Data Center, the Pearl Project, the University of Miami, and the Florida Neonatal Neurologic Network (FN3). The FL-DECADE team also partners with several organizations across the state, including treatment and support programs for mothers who use opioids. Within the Gainesville area, existing coalitions work with this population, and one has developed a peer-parent model that is now being translated to other Healthy Start coalitions across the state. FL-DECADE will be advised on retention issues by investigators involved in prenatal cocaine cohorts in Miami and Gainesville.

Aim 1 of the FL-DECADE study is to develop a comprehensive understanding of legal, ethical, and pragmatic factors that impact effective recruitment and retention of high-risk participants in longitudinal research. The study team will hold a summit, "Legal, Ethical and Pragmatic Considerations for a Prospective Cohort: Minimizing Risks and Maximizing Benefits," in spring 2020. Florida has established an early childhood courts system across the state with the goal of minimizing separation of mother and child during the first 2 years of the child's life. The planned FL-DECADE summit will address potential legal, ethical, and pragmatic issues the study team is likely to face. The team also plans to hold a focus group study of pregnant women and mothers.



FL-DECADE will also 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 (Aim 2). The Department of Health Outcomes & Biomedical Informatics at UF houses OneFlorida, a network of health care systems with state agency and organization collaborators whose main purpose is secondary data analysis. This system provides an existing structure for recruitment. The study team will also conduct direct recruitment and use recruitment-driven sampling to identify pregnant women using substances who are not in treatment.

To address Aim 3, FL-DECADE will obtain assessments during pregnancy and the neonatal period and leverage existing data across early childhood; the FL-DECADE study group will then conduct a pilot study with approximately 40 participants. In this study, investigators will collect drug-exposure information and obtain structural MRIs from infants at birth. The FL-DECADE team hopes to recruit women from FN3 network sites and use previously standardized protocols. The team will also work with members of the ABCD Study. The FL-DECADE group intends to expand current efforts across Florida to determine whether the use of a statewide network of linked school and environmental data can supplement data collection.

Discussion

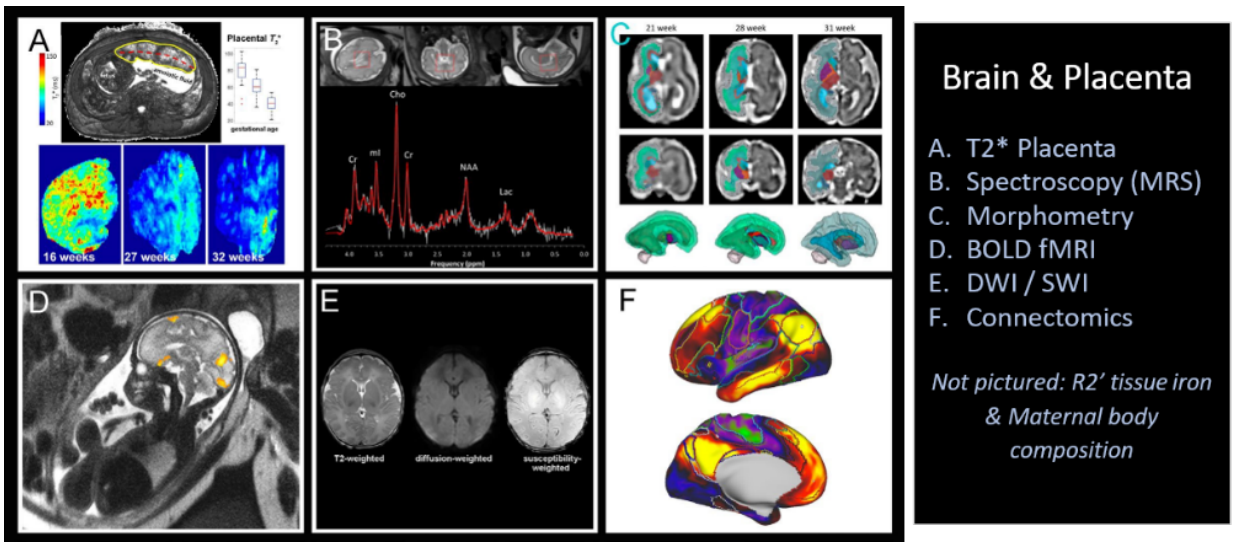
Dr. Deoni noted that the investigators might want to consider integrating across HBCD Phase I teams to determine what advantages and trade-offs are of different approaches. Dr. Freund indicated that this possibility is precisely the point of the working group discussions.

Dr. Volkow reiterated that the exploration mode of Phase I is intended to provide opportunities to compare strategies and methodologies. She asked Dr. Gurka why the FL-DECADE would include only structural imaging. Dr. Gurka indicated that this was selected based on the existing FN3 protocols.

Dr. Ossorio asked whether specific consent had been given for linking of health data to educational data. Dr. Gurka indicated that OneFlorida has an elaborate consent process for health data. Dr. Ossorio noted that there are laws regarding privacy of children's educational information. Dr. Fallin reported that there are some examples of successful data linkages in Baltimore.

Investigation of OPioid Exposure and Neurodevelopment (iOPEN) *(Moriah Thomason)*

Moriah Thomason, Ph.D. *(New York University)*, presented an overview of the iOPEN project, which includes investigators from the University of Pittsburgh, Oregon Health and Science University, New York University School of Medicine, and the University of Vermont.



The study includes aims addressing recruitment, imaging, and biobehavioral protocol feasibility as well as data processing and quality. Aim 1 is to evaluate innovative recruitment and retention strategies for long-term study of pregnant women and their children. The team will conduct pre- and postnatal surveys across a wide range of demographics to learn about women's research literacy and preferences as well as methods for engaging fathers. Surveys will be administered to approximately 150 women per site (cohort N~600, half with a history of opioid use during pregnancy), and findings will be broken down by income level, demographics, drug use, diagnoses, and treatment received in the past year.

Aim 2 is to implement a multisite longitudinal MRI and biobehavioral protocol. Each site will recruit 20 pregnant women and image pre- and postnatally to acquire images of placentas, fetuses, and neonates. In addition, each site will collect biospecimens from mother and child and behavioral data from mothers and fathers. Sites will also recruit five 24-month-old children (cohort N~20) with a history of opioid exposure and perform cross-sectional analysis.

Aim 3 will evaluate data acquisition, processing, and statistical considerations to maximize quality and integration across sites. There are a number of knowledge gaps regarding the imaging of infants and children, including how many minutes of scanning is necessary to obtain usable data and how to deal with motion. Aim 3 will focus on the development of novel imaging acquisition parameters and analytic pipelines.

Discussion

Dr. Volkow asked whether placental imaging would be necessary. Dr. Thomason noted iOPEN hopes to incorporate measures of the placenta that will add to what is known about brain development. The team also intends to assess maternal body composition and adiposity as well as fetal organ size.

Dr. Volkow indicated that she was oscillating between what could be learned from the placenta and the possibility that adding too much complexity could threaten the feasibility of this study. Dr. Thomason noted that there were imaging options that would add less than 4 minutes to scanning time. A cost-benefit type analysis could then be conducted on the contributions of the additional data.

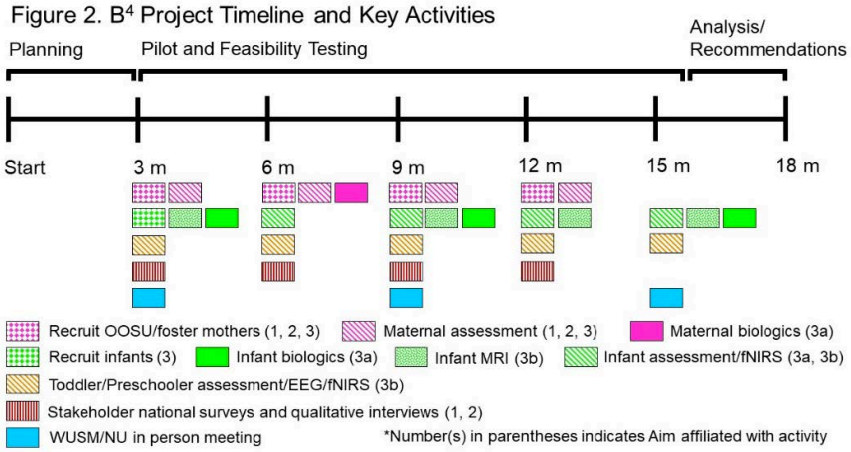
Dr. Spong expressed her belief that the placenta is an essential source of information. Dr. Volkow stated that in studying a very large cohort it is easy to get overwhelmed by the possible data points and that it will be important not to try to answer too many questions at once. Dr. Thomason indicated that the key issue regarding placental measures is whether or not what is being measured will be useful or contribute in unforeseen ways.

Optimizing Access, Engagement, and Assessment to Elucidate Prenatal Influences on Neurodevelopment: The Brains Begin Before Birth (B^4) Midwest Consortium *(Cynthia Rogers)*

Cynthia Rogers, M.D. *(Washington University)*, described the B^4 research team, which includes legal expertise in Illinois and Missouri, expertise in child welfare, high-risk longitudinal studies, neuroimaging, perinatal substance use assessments and risk-prediction. The team is organized into working groups. Study partners include recruitment and treatment sites and the State of Missouri Department of Social Services.

The B^4 consortium is unique in that Missouri is a non-punitive state where prenatal substance use does not have a mandatory reporting requirement and pregnant women are given substance misuse treatment. Illinois is not a non-punitive state, and the B^4 team believes that qualitative interviews at both sites (Washington University in Saint Louis and Northwestern University) can provide valuable information. These interviews, combined with national surveys of clinicians and scientists in other contrasting jurisdictions, will contribute to study Aim 1: to examine research and clinical implications of state-level differences, to deliver best practices recommendations for study design and state-based comparisons.

Figure 2. B^4 Project Timeline and Key Activities



Aim 2 of the B^4 project addresses the challenges of recruiting and retaining pregnant substance-using women by using community treatment centers and non-treatment-seeking women in the community. The B^4 team will design recruitment flyers and use eye tracking to measure attention and interest in recruitment materials. The group will employ an app called "uMAT-R" for perinatal women with substance use disorder to provide features like videoconferencing, appointment reminders, and treatment supports. B^4 researchers will evaluate whether these strategies to engage high-risk pregnant women result in increased retention.

The third aim of the B^4 Phase I project is to generate a protocol for exposure, imaging, and other developmental and psychosocial assessments. The team will query the willingness of mothers to participate in biological sampling methodologies and determine whether it is possible to identify fathers. The B^4 group will

also ascertain the feasibility of obtaining EEG, MRI, and fNIRS data in 3, 6, 12 and 24-month-old children in both the lab and community. These data will be combined with existing data sets on maternal stress, mental health, and multiple MRI time points.

The Cumulative Risk of Substance Exposure and Early Life Adversity on Child Health Development and Outcomes *(Amy Elliott)*

Amy Elliott, Ph.D. *(Avera Research Institute)*, introduced members of the Cumulative Risk of Substance Exposure and Early Life Adversity on Child Health Development and Outcomes consortium from Women and Infants Hospital Rhode Island, Father Flanagan's Boys' Home, the University of Maryland, Boston Children's Hospital, and Avera Research Institute. Participating sites provide access to a range of locations and populations, including Dr. Nelson's cohort of non-substance-exposed individuals with high social stress. Consortium members contribute experience with bringing 3T and low-field imaging from the lab to the bedside, using EEG and MRI, and statistical frameworks for longitudinal neuroimaging and neurocognitive data.

Each site has two to three different cohorts of different developmental time periods, from 22 gestational weeks to 4 years old, that will contribute up to 400 participants across the consortium. Maternal and fetal assessments will include family history/demographics, mental health, nutrition, anthropometry, body composition, metabolic rate, cognition, prenatal MRI, fetal ultrasound, sleep and autonomic measures, and biosamples. Infants and children will be evaluated using MRI; EEG; fNIRS; biosamples; the MSEL; and measures of deferred imitation, eye tracking/attention shifting, hearing, nutrition, anthropometry, metabolic rate, sleep, and autonomic functioning.

Discussion

Dr. Volkow queried whether there is the potential for MRI evaluations at the South Dakota site. Dr. Deoni indicated that the team is currently working with General Electrics to put two new high-gradient-strength pediatric scanners into mobile trailers to provide imaging access at all locations.

Planning for the HEALthy Early Development Study *(Christina Chambers)*

Christina Chambers, Ph.D. *(UCSD)*, provided an overview of the five-site (Case Western Reserve University [Case Western], Oklahoma State University [OSU], UCSD, Emory University [EU], and the University of New Mexico [UMN]) planning for the HEALthy Early Development Study Consortium. The consortium has established 10 working groups to cover topics in planning and protocol development. The team will investigate substance exposure and identify substance use assessments that work best using focus groups of mothers. Sites will also assess the feasibility of imaging and developmental assessments at various time points in children aged 1-24 months, best practices for biospecimen collection, and develop a protocol for the use of novel technologies.

The Case Western site plans to conduct additional pilot studies including magnetic resonance fingerprinting, which allows simultaneous quantification of multiple imaging properties from a single 4-minute scan.

The Emory research team will pilot innovative methods for assessing infant cognition and reward processing. The EU team includes Judge Peggy Walker, who works with women in the court system.

The OSU research team will perform assessments at birth and 1, 6, 12, and 18 months of age, including measures of cognition, motor abilities, language, and emotional arousal, as well as placental and meconium sampling.

The UCSD team will pilot crib-sensor technology for cardiorespiratory function. The UCSD team will also evaluate the impact of MotherToBaby Pregnancy protocols and access to the MotherToBaby Counseling network on recruitment and retention, as well as devise a breastfeeding assessment and 3D facial image capture.

UNM is responsible for harmonization across the five sites and providing a single IRB to the consortium and plans to examine the feasibility of recruiting from rural and underserved areas. The UNM research team will pilot pediatric MRI and EEG methods and will link epigenetics and neuroimaging data.

HBCD Working Groups *(Michelle Freund)*

Michelle Freund Ph.D. *(NIDA),* introduced this discussion by identifying five proposed overarching workgroups to help inform the Phase II HBCD Study. The topics were gleaned from the HBCD Phase I project applications and include: (1) Study Design, (2) Ethical & Legal Issues, (3) Biospecimens, (4) Non-Imaging Assessments, and (5) Imaging Assessments. As needed, subgroups to these working groups might also be formed. The working groups should span the 29 funded applications, and are charged with examining experimental approaches, obstacles and ways to overcome them, and feasibility of assessments, recruitment strategies, community engagement, etc. They are not expected to arrive at a consensus protocol; however, the goal is to ensure that diverse approaches have been vetted so that their strengths and weaknesses are identified, which will inform protocol recommendations for the Phase II project.

The Study Design working group will address topics such as community engagement, recruitment of vulnerable populations, different sampling strategies, and risk prediction methods.

The Ethical & Legal Issues working group will focus on issues including reporting laws, considerations regarding risks/benefits to study participants; access to treatment or services, relationships with CPS, certificates of confidentiality, data sharing, and the engagement of family members and others.

The Biospecimens working group will address matters such as self-report of drug use and other stigmatized behaviors, toxicology, use of geocoding, and which biospecimens to collect and when.

The Non-Imaging Assessments working group will identify which measures are most reliable for participants in the HBCD age groups, as well as frequency of assessment. Among the measures to be considered (for the parent and/or the infant) are: mental health, cognitive, motor, socioemotional, environmental measures; wearables and new technologies; the Global Scale for Early Development; and the NIH Infant and Toddler Toolbox (if available).

The Imaging Assessments working group will focus on data harmonization, multimodal imaging, and data-sharing principles.

If HBCD consortium members have suggestions for additional working groups, discussion is encouraged. Program staff intend to assist in providing a shared workspace like the NIH Box.

Discussion

Dr. Spong thanked Dr. Freund for suggesting fundamental workgroups for the consortium and indicated that she would like the group to discuss them for the planning phase as a whole.

Dr. Thomason offered to share the list of potential workgroups her group had developed.

Dr. Charness suggested the group consider including a workgroup for organizational structure, governance, and risk management. Dr. Freund agreed.

Dr. Fallin asked whether access to treatment could be assigned to the ethics workgroup. She noted that biospecimens could be addressed by any group and could be considered outcome measures.

Dr. Volkow proposed the inclusion of a workgroup for data architecture and structure, to address issues of confidentiality, blending and harmonization of databases.

Katia Delrahim-Howlett, Ph.D., M.P.P., M.B.A. *(NIDA)*, indicated communication and outreach might fall into any of the workgroup categories, but that NIDA had envisioned it for the legal and ethical issues group.

Dr. Weiss stated that, in defining the basic working groups, NIDA staff had collapsed many potential groups. She emphasized that this list was compiled not to dictate topics or structure to the group, but to share what NIDA has identified as some of the most critical issues investigators have raised.

Dr. Spong noted that it will also be important for investigators to consider what is feasible. She queried whether the NIH wants the HBCD consortium to weigh in on issues of structure and governance. Dr. Freund indicated that the NIH does not intend for Phase I to dictate structure and governance. Dr. Spong suggested that structure and governance will be the responsibility of an NIH workgroup.

Dr. Elliott asked who would be responsible for coordinating working groups. Dr. Weiss stated that grantees will coordinate with one another, given that HBCD Phase I is an "R" grant and not a cooperative agreement. Dr. Delrahim-Howlett clarified that the investigators would organize meetings and support logistics for Phase I, but that NIDA could provide some additional support if needed.

Dr. Ossorio reported that she had budgeted for monthly ethics discussions among Phase I PIs. She further noted that many of the Phase I grantees have included qualitative studies to evaluate ethical, recruitment, and retention issues and that including some common questions could be helpful.

Dr. Spong noted that all Phase I projects are robust, and redundancy will enhance reproducibility. She indicated that it would be helpful to know how much the NIH expects to be fleshed out in 18 months.

Dr. Volkow explained that the HEAL Initiative has a very different review process than other initiatives at the NIH. To increase the likelihood of funding for Phase II, NIDA and its contributing institutes, center and office partners need to demonstrate the feasibility of the study as well as preparedness to address challenges based on Phase I data. She advised the group to concentrate on research that will produce evidence of feasibility and pilot results.

Dr. Fair noted that it will be important to establish deliverables for each working group. Dr. Fair further indicated that the workgroups create economies of scales and avoid duplication of work. Dr. Freund agreed, noting that this was the primary reason sharing of protocols will be helpful.

Dr. Lin pointed out that the NIH has provided guidelines about the Phase II study, including that it be longitudinal, and it provide numbers for recruitment and follow-up, but not all recruitment protocols will be reasonable for all sites. Dr. Freund agreed, noting that the number of 7,500 participants is an approximation and that NIDA and its partners hope to learn what is feasible from Phase I grantees.

Dr. Weiss noted that it may not be feasible to structure the HBCD Study in the same way as the ABCD Study. Recruitment for the HBCD Study may require a "hub-and-spoke" arrangement to reach different populations with limited resources. Although a common protocol for Phase II is the ultimate goal, NIDA and its partners are looking for input on this from working groups on how to conduct the HBCD Study.

Hugh Garavan, Ph.D. *(University of Vermont)* asked if Phase II will use a common protocol with individual protocols for specific research at different sites. Dr. Volkow noted that although these data have an enormous amount of value, funding is limited. She suggested the group consider what the goals are and how to achieve them. The team will want to maintain an adaptive ability to incorporate new components but should remember that it is not possible to do everything.

Dr. Garavan asked whether working groups should be establishing a common core protocol. Dr. Freund indicated that working groups are to ensure that Phase I investigators are talking to and learning from one another. The working groups and Phase I research may identify approaches that are not feasible, but Phase II should have options. Dr. Volkow agreed, noting that NIDA and its partners wants to learn from investigators, as they are in the best position to determine what is achievable.

Dr. Deoni asked whether the deliverables needed to support Phase II funding are all evidence of feasibility. Dr. Spong noted that the goal is to demonstrate the strengths and weaknesses of different methods. The pilot phase will show how strategies have been tested and which worked at each site.

Dr. Spong asked whether Dr. Volkow wants prenatal imaging studies done in the planning phase of the HBCD Study. Dr. Volkow indicated that this had been discussed and that not all sites are capable of obtaining reproducible prenatal images. Dr. Volkow stated that her goal is to examine the quality of measures from the neonatal phase of development onward and determine which measures can

assess the phenotypes of behavior that will help to create a knowledge base. It will be important to justify to members of the scientific community why this study is being conducted. She indicated that all investigators will have to identify which measures and data are indispensable.

Dr. Panigrahy queried how NIDA and other institutes would use Phase I data to create a protocol. Dr. Volkow indicated that during the planning of the ABCD Study, experts were brought together to determine the best methodologies, which were presented to respective advisory councils for feedback. Dr. Panigrahy questioned whether NIDA will want recommendations on "space-age assessments." Dr. Spong indicated that NIDA wants to know what methods and assessments work best and options to consider for a common protocol. Dr. Freund stated that NIDA and its partners are looking for evidence and recommendations that can be used to create the best possible funding opportunity announcement for Phase II.

Dr. Deoni proposed a working group to aggregate information from other groups. Dr. Spong indicated aggregation would occur in two HBCD PI meetings and encouraged participants to meet as often as possible.

Gaya Dowling, Ph.D. *(NIDA)*, reported that the workgroup categories included consideration of what was proposed and how participants could collaborate. The individuals responsible for gathering the data from each group and identifying what is being decided should be embedded within each group.

Dr. Deoni asked what the ABCD Study uses for a communication platform. Dr. Jernigan reported that the ABCD Study primarily utilizes Confluence; the ABCD project holds many teleconferences but uses Confluence to share everything. Dr. Delrahim-Howlett indicated that the HBCD Study will use NIH Box.

Ludmila Bakhireva, M.D., Ph.D. *(University of New Mexico)*, pointed out that another aim of the HEAL Initiative is to inform interventions. She asked how the NIH envisions this occurring. Dr. Volkow noted that one key aspect of the ABCD Study has been the release of data as soon as quality control is complete, so that the information is available to inform interventions. This will be equally important in the HBCD Study, so that data on developmental deviations are available as soon as possible to facilitate interventions. Dr. Deoni noted that the group will face the same ethical issues as the ABCD.

Dr. Garavan noted that there are not a lot of resources available to support the working groups. He also reported that ABCD investigators spent a lot of time attempting to counter messaging that the ABCD Study was a study of drug misuse, to support recruitment. He suggested that because 85 percent of the HBCD cohort will be non-opioid-using, the group should think ahead about messaging. Dr. Volkow echoed this sentiment, indicating that NIDA and its partners are very sensitive to this issue.

Dr. Dowling noted that Dr. Rogers and others had discussed development of recruitment materials and that demonstration of the efficacy of these materials will provide persuasive data on recruitment feasibility.

Wrap-Up *(Michael Charness)*

Dr. Charness indicated that conducting the ABCD and HBCD Studies simultaneously is analogous to the creation of the transcontinental railroad, starting at opposite ends and working toward the middle. The ABCD Study follows children from ages 9 and 10 to adulthood, and the HBCD Study will begin prenatally and follow participants until ages 9 to 10 years. The studies will critically contribute to the understanding of neurodevelopment.

Dr. Charness believes the complexity of the HBCD Study is much greater than that of the ABCD Study. Collegiality and collaboration in the ABCD Study informed grantees' sense of mission and purpose. This will be even more important in the HBCD Study. This study is different because at least 15 percent of children will have had serious prenatal exposures. The complexities contributed by other adverse childhood experiences will make it challenging. This study is also different in that people have very different expertise. The heterogeneity

of the grantees, combined with geographic diversity, underscores the importance of arriving at common language, definitions, protocols, motion adjustment, and harmonized imaging for Phase II success.

The 18-month planning period is something that the ABCD Study did not have. There was a great deal of discussion in HBCD planning meetings regarding how easy it is to image infants but not motile children, as well as the appropriate time intervals to do different evaluations. The pilot studies will be critical to understanding what is feasible in Phase II. Ethical issues will be the most challenging and the most critical to address; inherent in solving these challenges are recruitment and retention and other key issues that will impact participants.

In the HBCD planning meetings, there were two perspectives on these issues. One perspective was that altruism is sufficient to encourage participation and it is not necessary to provide other benefits. The second perspective was that mothers are putting themselves, their children, and their ability to raise their children at risk. It is important to determine how to balance risk from study participation and substance misuse with potential benefits.

It will be important to examine the differences in statutes across states and consider a common approach to negotiating with state attorneys general. The HBCD consortium should capitalize on investigators with expertise in legal and ethical matters and consider challenges such as successors to attorneys general.

The HBCD Study is no less feasible than the ABCD Study. There will be challenges, but the opportunity to produce a brain and development map from birth to adulthood is unique. The HBCD Study also has an opportunity in terms of messaging. This is a unique opportunity to do something for the world.

Dr. Volkow thanked Dr. Charness for summarizing the importance of the HBCD Study and emphasized her commitment to making the study happen. Other NIH institute/center/office directors have been extremely supportive. All are aware of how important early life experiences are to overall health. NIDA wants to work with grantees to figure out how to design the HBCD Study to succeed. Dr. Volkow stressed the availability of program staff to investigators, reminding participants that NIH wants investigators to succeed. NIDA and NIH are committed to making these data available and investigators should feel free to share information and perspectives. Dr. Volkow closed by thanking all who have worked to make this project happen.