Eunice Kennedy Shriver
National Institute of Child Health and Human Development (NICHD)
National Institutes of Health (NIH)

2020 Best Pharmaceuticals for Children Act (BPCA) Stakeholders Meeting

December 14–15, 2020

Meeting Summary

Purpose. The purpose of this meeting was (1) to provide updates on the Best Pharmaceuticals for Children Act (BPCA) Clinical Program, at the National Institutes of Health (NIH) and (2) spearhead the development of a roadmap for identifying needs, prioritizing those needs, and for closing knowledge gaps in pediatric therapeutics that are applicable to a variety of stakeholders involved in pediatric drug development.

Day 1: Monday, December 14, 2020

Welcome, Introductions, and Overview of Meeting Goals

Perdita Taylor-Zapata, M.D.
Program Lead, Physician
Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB), NICHD, NIH

Aaron Pawlyk, Ph.D.
Chief, OPPTB
NICHD, NID

Dr. Taylor-Zapata opened the meeting by welcoming participants and thanking them for their continued interest in, and contribution to, the BPCA Program. She emphasized that the first day of the meeting would provide an opportunity not only to report on current work within the BPCA Program, but also provide a forum for participants to share their knowledge and experience in identifying and addressing challenges in pediatric drug development and therapeutics. Dr. Taylor-Zapata also emphasized that during the Day 2 roundtable/breakout sessions, participants would have the opportunity to describe/discuss some of the challenges they have faced and share lessons learned from their work in pediatric drug therapeutics. She also offered that this meeting provided a forum to foster collaboration among meeting participants and their stakeholder colleagues.

In his welcome remarks, **Dr. Pawlyk** pointed out that the key research themes/goals of the 2020 NICHD Strategic Plan are particularly relevant in the current COVID-19 scientific environment. He also noted that one of the key elements of the Plan emphasizes NICHD's mandate to ensure development of safe and effective therapeutics for women and children. He encouraged participants to share their experiences and identify areas for collaboration and alignment with the NICHD Strategic Plan during Day 2 roundtable discussions. He thanked attendees, noting that

their input would provide invaluable assistance to NIH/NICHD in advancing/revising the Institute's Strategic Plan during this very "unusual" year.

Dr. Taylor-Zapata presented a brief overview of the BPCA legislative mandates and the separate, yet parallel, relationship with the U.S. Food and Drug Administration (FDA). She reiterated that the NIH focus is on off-patent drugs, and the FDA focus is on-patent drugs. She next summarized the key NICHD responsibilities in pediatric drug development under the BPCA Program:

- Prioritize needs in pediatric therapeutics.
- Sponsor clinical trials through the Pediatric Trials Network (PTN), also through pharmacology training programs and translational research.
- Submit data to FDA and public domain [Data and Specimen Hub (DASH)].
- Improve drug labeling.

Dr. Taylor-Zapata noted that under the BPCA Program at NICHD, to date, 200 drugs and 50 therapeutic areas have been prioritized. In addition, 44 clinical trials have been conducted, and 28 clinical study reports (CSRs) have been submitted to FDA for labeling changes. She presented examples of pediatric drug label changes from 2012 to the present. Dr. Taylor-Zapata stressed that this is a complex, arduous, and time-consuming process. She also briefly described the BPCA Program, including the Pediatric Research Equity Act (PREA), again emphasizing that prioritization is a lengthy process with many complex components. In addition to NICHD, stakeholders included NIH liaisons and FDA. Their input was incorporated into the BPCA annual priority list. Dr. Taylor-Zapata referred participants to the BPCA website for more detailed information.

Dr. Taylor-Zapata reiterated that Day 1 discussion would focus on clinical trials implementation, with an overview of the PTN activities over the past 10 years. With an emphasis on creativity and innovation, the PTN has supported and encouraged implementation of practical study designs, as well as pediatric drug development without drug developers.

She also noted that during Day 1, the BPCA Data Coordinating Center (DCC), EMMES Corporation, would discuss key study elements, especially pertinent and more complicated in light of the current global pandemic:

- Data capture
- Study and safety monitoring
- Data quality
- Regulatory support
- FDA submission.

Dr. Taylor-Zapata closed by reminding participants that Day 1 discussions also would include updates from PTN leadership, as well as plans for increased stakeholder future involvement.

Triumphs and Trials in Pediatric Therapeutics — Perspectives from the PTN and EMMES DCC

Danny Benjamin, M.D., Ph.D., M.P.H.
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Kiser-Arena Distinguished Professor of Pediatrics
Department of Pediatrics, Duke Clinical Research Institute
Pediatric Trials Network, Duke University Medical Center

Kanecia Zimmerman, M.D., M.P.H.
Assistant Professor of Pediatrics
Department of Pediatrics, Duke Clinical Research Institute
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Ravinder Anand, Ph.D.
Vice President & Biostatistician
The EMMES Corporation/BPCA Data Coordinating Center

Gina Gorgone Simone
Project Director
The EMMES Corporation/BPCA Data Coordinating Center

Dr. Benjamin reiterated the PTN mission and purpose: to create an infrastructure for investigators to conduct trials that improve pediatric labeling and child health. Sponsored by NICHD, for more than 10 years, the PTN has focused on improving dosing, safety information, and labeling in off-patent therapeutics. Dr. Benjamin briefly reviewed the original PTN Scope of Work: to conduct 16 clinical trials (mostly Phase 1 and Phase 2 studies) in 6 therapeutic areas; enroll 1,600 children and manage 4 product submissions. As of this date, PTN studies cover 18 therapeutic areas; more than 11,000 children have been enrolled in PTN studies. A total of 26 submissions have been made to FDA, resulting in 15 label changes.

Dr. Benjamin introduced **Dr. Zimmerman**, who discussed the myriad challenges to developing and conducting pediatric clinical trials between 2010 and 2018. She listed the following challenges, as well as briefly described some of the methods that the PTN implemented to help meet these challenges:

- Limited number of patients
- Limited blood volume
- Competing research priorities
- Low consent rates
- Onerous contacting and start-up process
- Lack of trained pediatric clinical investigators
- Lack of pediatric clinical pharmacology expertise.

Dr. Zimmerman next pointed out that within the past 2 years, developers of pediatric drug studies have also faced new and emerging challenges. These new challenges include:

- New populations
- Lack of validated endpoints
- Need to expand to new therapeutic areas.

Dr. Zimmerman pointed out that meeting those challenges has been even more complicated due to two public health "crises"— hospitals with competing financial priorities and a limited number of available pediatric study investigators.

She then briefly described some PTN-supported studies and how they have met some of these challenges, in new populations, such as children with Down Syndrome (DS). She described the INCLUDE Project, in particular, the Guanfacine for Hyperactivity in Children with Down Syndrome (HYPEbeGONE_DS) Study. This prospective, multicenter, randomized trial studied the clinical diagnosis of non-mosaic DS. The goal of the study was to promote bidirectional learning among new investigators and multiple advocacy groups on how to conduct clinical trials and meet regulatory compliance within this new study population.

Dr. Zimmerman next summarized several current and new studies designed to meet and overcome some of these key and emerging challenges. She described the Pharmacokinetics and Safety of Commonly Used Drugs in Lactating Women and Breastfed Infants (CUDDLE). PTN investigators developed an opportunistic master protocol to study lactating women receiving drugs of interest per the standard of care. Dr. Zimmerman also pointed to the challenge of endpoint validation for pediatric clinical trials. She cited the anesthetics and analgesics master protocol as an example of collaboration with FDA and developers of the original sedation scales. Dr. Zimmerman also noted that the PTN has identified methadone as an issue for submission to FDA. Although increasingly used to manage pain in children undergoing surgical procedures, methadone is currently only labeled for adults.

Dr. Zimmerman next discussed terbutaline. This potentially life-saving therapy is used to treat children with critical asthma. PTN is collaborating with FDA to conduct the Cross-Over Trial of the Exposure-Response Relationship of Terbutaline Sulfate in Adults with Asthma (TBS02).

Dr. Zimmerman emphasized that the need to study child health has become even more critical given the current and anticipated future COVID-19 environment. She presented a dashboard that highlighted key events/milestones between March and June 2020 that NICHD used to plan for and address the need to update study protocols and to adapt NICHD/PTN specialties and expertise to address the current public health crisis. She suggested that researchers consider doing research differently, for example, adapting the LAP01 trial protocol to COVID-19 dynamics.

Dr. Zimmerman addressed the recent attention on disparity. Within the current era of racial awareness, NICHD conducted an assessment of potential racial and ethnic bias in enrollment in

PTN studies. Dr. Zimmerman explained that while final results are currently under review prior to publication, preliminary results have indicated the following:

- Minority enrollment in PTN studies was comparable to, or higher than, expected for all groups except Asian children.
- Enrollment among American Indian/Alaska Native and Multi-racial children significantly increased over the evaluation period.
- No significant differences were found in racial distribution as a function of age or sex.

Dr. Zimmerman suggested as a next step that stakeholders should develop a pipeline that builds on programs and relationships, such as the R25 program, current collaborations with Biogen, and community engagement activities such as those supported by the ABC Science Collaborative. Using these resources and relationships is an efficient and effective way for PTN to establish and maintain a standardized nationwide structure to investigate new drug development.

Dr. Anand described the key role played by the EMMES Corporation in supporting the BPCA DCC. The EMMES Corporation partners with the PTN in study protocol development, as well as data collection and management. The DCC also works with study sites to ensure pharmacologic and medical compliance. DCC site monitoring includes assisting in FDA audits. In addition to statistical analysis, the DCC assists in preparing approximately 135 regulatory submissions per year. Dr. Anand explained that DCC support to the BPCA PTN typically includes the following:

- Coordinating approximately 25 simultaneous new drugs investigations
- Enrolling participants in 5–10 studies, conducted in more than 250 sites
- Developing 2–5 new protocols
- Preparing 3–5 CSRs.

Dr. Anand further noted that this support has resulted in 11 label changes and 2 marketing approvals.

Ms. Simone explained that the approach to managing a consortium such the PTN is considerably different from managing support for a single study. Helping ensure consistency and standardization across the PTN involves developing and using efficiencies throughout PTN study sites. The DCC has helped promote, develop, and maintain templates for protocols and informed consent forms, as well as centralized master protocols. Equally important, the DCC has helped standardize data elements and data collection methods. The DCC also supports efficient tracking and management of study specimens maintained in biorepositories to help inform future research.

Ms. Simone emphasized the importance of a centralized website in promoting ongoing communication and information-sharing, including data collection, among study sites and PTN leadership. She noted that some study sites use web reports to post daily (or nightly) updates to PTN and NIH.

Ms. Simone agreed with other presenters that research in pediatric populations presents unique challenges that could impact protocol implementation and data collection. She described tools such as eConsent and waivers from written consent, which are critical for neonatal studies, including studies in response to COVID-19. Ms. Simone also noted that in March 2020, researchers adapted consenting tools from a current study (POP02) to add drugs known to treat COVID-19 to acquire critical data and specimens in pediatric populations.

Ms. Simone discussed the challenge of maintaining participant enrollment during the periods of inactivity that are typical in pediatric studies. She again recommended using a central website to keep stakeholders alert to activities in other study sites. She also recommended conducting monthly "all site" virtual meetings, where participants could post and view meeting slides and listen to recordings.

Ms. Simone also noted that long before COVID-19, NICHD has been addressing the issue of monitoring while simultaneously implementing study protocols, especially challenging in pediatric studies. She explained that pediatric studies typically require three to five times as many sites to enroll the same number of participants as in adult studies. Therefore, study developers need to identify various methods for remote monitoring. In addition to direct access to site electronic health records (EHRs), Ms. Simone described other methods for remote monitoring, for example, electronically maintained Investigator Site Files, which allow for secure upload of site source records, as well as virtual site "tows" and data "walk throughs."

Ms. Simone also briefly discussed other challenges to developing pediatric studies. She explained that because most BPCA study participants have pre-existing conditions, determination of adverse events (AEs) is a significant challenge for pediatric studies. In most BPCA studies, AE reporting is restricted to deaths. She described events of special interest (ESIs). She noted that the specific "yes"/ "no" ESI format helps ensure consistency and uniformity in safety data collection across study sites. ESIs also promote study efficiencies and help sites avoid time and effort in collecting unnecessary and irrelevant information.

Dr. Anand also noted that the goal is to design studies that reduce the burden on clinic staff, while at the same time, design studies to better align with clinical care and reduce protocol deviations. He stressed the need to involve both clinicians and coordinators in consulting on study logistics.

Dr. Anand explained that the BCPA uses Master Protocol Design (MPD) to support investigation of numerous drugs of interest (DOIs), which are identified on the BPCA priority list. He noted that the MPD model has been successful in supporting rapid enrollment and acquisition of data on a large number of DOIs concurrently being studied under a single project. Dr. Anand also noted that the MPD approach has the potential to increase a program's productivity and success in achieving label changes without compromising data quality.

Dr. Anand presented an overview of the first PTN master protocol (POPcx1). First launched by PTN in 2011, this master protocol (MP) enrolled 3,500 participants under 70 DOIs. Since inception of the first MP, the PTN has added four other MPs. Improvements to the MP include

more effective data system design and efficiencies in support of analysis and regulatory activities. Currently, the PTN is developing a new MPD that will focus on multiple investigations of infants receiving drugs for specific indications.

Dr. Anand discussed clinical study requirements and regulatory review. He explained that before submission to FDA, a BPCA PTN CSR typically combines data from multiple studies. He also pointed out that there has been evolution in the submission and review of BPCA/PTN data at FDA.

Dr. Anand next discussed the future direction of data collection in a post-COVID-19 environment. He noted that maintaining information in EHRs has the potential to ease the burden on study coordinators, as well as reduce overall costs without sacrificing data quality. He also suggested exploring the potential for remote data capture via Expanded Patient Reported Outcomes (ePROs) and through use of wearable devices to collect long-term data from children enrolled in PTN studies without compromising their daily activities. He reiterated that the emphasis is on identifying mechanisms and methods for conducting trials remotely. Dr. Anand again emphasized that the intent is to identify and adapt technologies and tools such as ePROs to reduce the burden on study patients and study participants, mostly focusing on population studies. The intent is to use the capabilities of these various tools for collecting data remotely to help ensure diversity in BPCA-sponsored clinical trials. Dr. Anand closed by emphasizing the critical role of the DCC in supporting regulated clinical trials in pediatric populations.

Questions and Answers

Dr. Taylor-Zapata read questions that participants had submitted during the course of presentations.

Question: You discussed leveraging standard of care in conducting these trials. Please elaborate on the pros and cons of using that type of trial design.
Answer: Dr. Zimmerman explained that this type of trial design limits the burden on study sites and on patients and their families. This type of trial design makes it easier to agree to consent for a child to be enrolled in the study. It also makes it easier for busy clinicians to serve as principal investigator. However, this type of trial is limited by the standard of care itself. At the same time, that standard of care may vary from one study site to another.

Question: Do you collect feedback on the acceptability of study drugs? If yes, is that information collected in a standardized way?
Answer: Dr. Zimmerman reiterated that the BPCA priority list is the source of identifying drugs being considered for PTN studies. Additionally, to study a drug, there needs to be a gap in the labeling along with a clear need to study the drug. Finally, there also must be the ability to use somewhat limited resources to conduct the study. For efforts such as the POP study, investigators were asked to indicate what drugs they recommended to be studied. Increasingly, investigators are being asked for their feedback regarding study protocols before a study design is finalized.

Question: Please discuss patient engagement, specifically, the role of parents. Do you involve parents in protocol development?
Answer: Yes. Dr. Zimmerman explained that some parents have demonstrated commitment to, and trust in, PTN protocols. The PTN welcomes and encourages their involvement. For example, for the DS study protocol, investigators definitely want to engage a diverse pool of parents and solicit their input during study conduct.

Question: Are there issues regarding data quality? For example, EHRs are notoriously "error prone," especially in collecting drug data and recording adverse events. How do you address those weaknesses?
Answer: Dr. Anand spoke for the DCC. He acknowledged that EHRs are the source for a large amount of information for these studies. To limit data entry from study coordinators (and thus minimize errors), the DCC recommends obtaining data directly from the EHR.

Question: Are you able to provide information regarding the iCAN group as a source of input from child patients?
Answer: Dr. Zimmerman explained that the PTN has been partnering with the iCAN group for the past year. She noted that the iCAN group has been extremely accommodating and that the partnership has been very positive. For example, iCAN child participants have served as reviewers for patient protocols. Dr. Taylor-Zapata mentioned that the NICHD Office of the Director has been working with iCAN to teach children about the peer review process.

Question: How does e-consent work in an inpatient setting? For example, does e-consent work for a study such as the inpatient preterm neonate study?
Answer: Yes. Ms. Simone emphasized that the DCC can offer e-consent for both COVID and non-COVID studies, including the POP02 study, across the PTN.

Question: How does the BPCA priority list relate to the World Health Organization (WHO) essential medicines list?
Answer: Dr. Taylor-Zapata explained that today's discussion focused on trials rather than development of the priority list. She noted that the list is an outreach tool available not only to BPCA stakeholders, but also to the WHO, advocacy groups, and industry. Dr. Taylor-Zapata pointed out these entities all provide input in development of the priority list. The BPCA program vets input from these sources to update and maintain the priority list. Historically, there has been some limited overlap between the WHO Essential Medicines List and the BPCA priority list. However, the overlap has primarily been in highlighting the need for more research in areas such as formulations in many infectious disease therapeutics.

Question: How do individuals become involved with the PTN?
Answer: Dr. Zimmerman recommended that individuals email the PTN Program Manager and posted the email address in the meeting chat box (PTN-Program-Manager@dm.duke.edu). She also explained that the PTN continuously maintains a list of current and new potential study investigators, noting their specific experience, capabilities, and topic(s) of interest relevant to the PTN. Dr. Benjamin pointed out that the PTN has made a commitment to the clinical

pharmacology community and specifically, to NICHD. He pointed to PTN's partnership with the R25 and T32 programs as well as with K23 awardees.

Dr. Taylor-Zapata described the BPCA prioritization process. She posted information in a chat on how to receive consultation from PTN via an X01 initiative titled "Catalyzing Innovation in Pediatric Pharmacology Clinical Trial Design and Resource Access." (https://grants.nih.gov/grants/guide/pa-files/PAR-20-161.html).

Regulatory Considerations for Addressing Needs in Pediatric Therapeutics

John Alexander, M.D.
Deputy Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research (CDER)
Division of Pediatric and Maternal Health
U.S. Food and Drug Administration (FDA)

Gilbert Burckart, Pharm.D.
Associate Director for Pediatrics
Office of Clinical Pharmacology
CDER, FDA

Dr. Alexander presented an update on the status of pediatric drug development and labeling for on-patent products in legislatively mandated programs, notably, BPCA and PREA. Currently, between 40 to 50 products are labeled each year. Dr. Alexander noted that as of April 2020, a total of 854 products have been labeled with pediatric-specific information. He explained that another 10 products are labeled under the NICHD-sponsored BPCA Program.

Dr. Alexander discussed FDA's role in responding to COVID-19. While this response is agency-wide, involving all FDA components, Dr. Alexander focused his discussion on the role of the FDA Vaccines and Related Biological Products Advisory Committee and CDER. He recommended that stakeholders access the FDA website (https://www.fda.gov/advisory-committees/advisory-committee-calendar) for more detailed information on the specific roles of FDA components in responding to the COVID-19 pandemic.

Dr. Alexander described the Coronavirus Treatment Acceleration Program (CTAP) (https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap). Designed to provide a rapid, coordinated response for drug developers, CTAP provides a centralized point of contact point for single-patient expanded access, drug development input, and protocol review. CTAP also coordinates redeployment of some medical and regulatory staff to support affected review divisions.

Most importantly, the CDER response to COVID-19 also addresses Emergency Use Authorization (EUA) for COVID-19 treatment/medical needs. CDER is also examining the effects of social distancing in clinical trial conduct and treatment protocols, as well as the impact of COVID-19 on completion of deferred studies required under PREA.

Dr. Alexander also discussed the Office of New Drugs reorganization. Recently completed in 2020, the reorganization affects 8 clinical review offices and 27 review divisions. The goal is to bring together staff doing similar and/or related work to promote information-sharing and streamline operations. Dr. Alexander described the new Office of Non-prescription Drugs, initiated under the Coronavirus Aid, Relief, and Economic Security (CARES) Act.

Dr. Alexander closed by reiterating that 2020 has been a challenging year with many lessons to be learned and issues (such as the effects of social distancing) that must be addressed in designing and conducting clinical studies and as a result of the response to COVID-19. He emphasized the need to be quicker and more nimble in planning for and responding to a public health crisis. Dr. Alexander cautioned that the effects of the COVID-19 pandemic on pediatric studies conduct and outcomes will continue for years. For example, FDA is already seeing delays in pediatric trials currently underway or studies still in the planning stage.

Dr. Burckart reiterated that accomplishing 854 label changes requires considerable scientific knowledge of drug use in pediatric populations. He noted that during the past 30 years, pediatric clinical study developers have continually faced the same or similar overarching issues. Dr. Burckart also described opportunities for addressing some of these issues among clinical scientists, industry, and regulatory agencies:

- Pediatric dosing: The Pediatric Dose Selection Workshop is a forum for advancing standardization of pediatric dose determination during drug development.
- Pediatric safety: Ongoing need to determine and study short-and long-term safety effects.
- Pediatric clinical drug simulations and trial design: Model- Informed Drug Development (MIDD) is used to estimate pediatric doses and exposures. A more complex and innovative trial design would benefit from adult MIDD study results. FDA will conduct a 2021 workshop on complex and innovative trial design.
- Studies in small/underserved pediatric populations: In a 2019 report to Congress on pediatric labeling of orphan drugs, FDA identified 27 orphan drug indications that were not fully labeled for pediatric populations.
- Fetal pharmacology: FDA guidance encourages inclusion of pregnant women in clinical drug trials, but the process for examining the disposition and effects of these drugs on the fetus is not clear. FDA reviewer guidance, Evaluating the Risks of Drug Exposure in Human Pregnancies dates back to 2005. New approaches to assessing fetal drug effects are needed.
- Pharmacogenomic studies: Currently, there is very limited information on the relationship between genotype and phenotype in youngest pediatric populations.

Dr. Burckart concluded by noting that much has been accomplished since 1997 when the challenges of developing new drugs in pediatric populations seemed insurmountable. Today, although these challenges can be managed and even resolved, they are still complex, demanding cooperation among funding and regulatory agencies, as well as collaboration among investigators, academics, and the pharmaceutical industry.

Questions and Answers

Question: Given the reorganization of CDER, is there an efficient mechanism to identify the most appropriate office to engage with regarding studies of psychotropic medications in children? For example, will there be an Office of Neuroscience or an Office of Research and Development in Pediatrics? What office should a colleague engage with regarding pediatric pharmacogenomics?
Answer: Dr. Alexander explained that the mechanism for engaging FDA will remain the same. The reorganization completed in 2020 dealt with Office of New Drugs (OND) Review Division. Questions related to psychotropic drug development should be submitted to the Division of Psychiatry within the Office of Neuroscience. Dr. Burckart pointed out that the Office of Clinical Pharmacology's recent reorganization parallels that of the OND. Also, the Office has groups that are active in pharmacogenomics.

NICHD and the Research Response to COVID-19

Rohan Hazra, M.D.
Acting Associate Director for Extramural Research
Division of Extramural Research
NICHD, NIH

Dr. Hazra began by pointing out that the NICHD response to COVID-19 is within the context of the history and mission of the Institute as well as the dynamics during the past 9 months. He reviewed the history and evolution of the NICHD, noting that NICHD remains committed to its original mission — to lead research and training to understand human development, improve reproductive health, and enhance the lives of children and adolescents. Dr. Hazra pointed out that the research themes presented in the 2020 NICHD Strategic Plan reflect the Institute's ongoing commitment to supporting that mandate. While the Plan defines several research themes, Dr. Hazra focused his remarks on one NICHD research theme in particular: Advancing safe and effective therapeutics and devices for pregnant and lactating women and children and people with disabilities.

Dr. Hazra cited several themes that cut across the PTN/BPCA Program agenda:

- Global health
- Health disparities
- Prevention
- Nutrition
- Infectious diseases.

He also pointed out that while NICHD is the largest supporter of pediatric research within NIH, it is far from being the only supporter. NICHD is already actively engaged in partnering and collaborating with other Institutes and Centers throughout NIH to address interdisciplinary challenges. Dr. Hazra described some of these trans-NIH COVID-19 activities and research efforts:

- NIH Pediatric Research Consortium (N-PeRC): Established in June 2019, N-PeRC is comprised of representatives from more than 40 NIH Institutes/Centers/Offices. Designated as the Consortium Lead Institute, NICHD oversees activities, such as managing transition to the adult health work group, expanding the pediatric research work group, managing pediatric data resources, and increasing the number of study section reviewers with child health expertise. N-PeRC also coordinates review/discussion of existing NIH pediatric programs and upcoming workshops.
  Dr. Hazra pointed out that N-PeRC's operational structure is already in place and tested, which has been invaluable in allowing NICHD to rapidly pivot to establish a trans-NIH response to COVID-19 that has been broadened to include pregnant and lactating women.
- Rapid Acceleration of Diagnostics (RADx): This group, and Accelerating Treatments in Vaccines (ACTIV), works to ensure that issues regarding the health and safety of children and pregnant women are addressed by other NIH groups. Dr. Hazra pointed out that the current Emergency Use Authorizations for the two COVID-19 vaccines do not include data on children or pregnant women.
- Clinical Trials Networks: These groups also foster cooperation and information-sharing to help ensure that researchers and study investigators are aware of the importance of NICHD populations.

Dr. Hazra next discussed COVID-19 other pending supplemental funding legislation:

- Coronavirus Preparedness and Response Supplemental Appropriations Act (CV)
- CARES Act (C3)
- Paycheck Protection Program and Health Care Enhancement Act (C4).

Dr. Hazra also described two other efforts:

- POP02: This sub-study focuses on characterizing the pharmacokinetics (PK), pharmacodynamics (PD), and safety of drugs for potential used for prevention or treatment of COVID-19.
- Multisystem Inflammatory Syndrome in Children (MIS-C): Clinicians initially thought that children were relatively spared from serious COVID-19. As the evolving nature of COVID-19 became more apparent from reports from the United Kingdom, Europe, and from some U.S. sites, it was clear that COVID-19 responses needed to include pediatric populations.

Dr. Hazra next summarized the goals for current and future COVID-19 pediatric research:

- Understand the range of clinical manifestations of SARS-CoV-2/COVID-19
- Understand the etiology and clinical manifestations of MIS-C
- Determine risk profiles for patients who develop MIS-C and/or severe COVID-19
- Understand variations in immune responses underlying the wide range of clinical manifestations in children infected with SARS-CoV-2
- Identify predictive and prognostic immune biomarkers

- Understand the long-term consequences of SARS-CoV-2, COVID-19, and MIS-C.

Dr. Hazra discussed supplementing existing programs, such as CARING for Children with COVID (Collaboration to Assess Risk and Identify Long-term Outcomes for Children with COVID-19). This collaboration with the National Heart, Lung, and Blood Institute (NHLBI) and National Institute of Allergy and Infectious Diseases (NIAID) is focused on coordinating data from three studies conducted by NIAID, NICHD, and NHLBI. He noted that data will be publicly available across three platforms:

- IMMPORT Shared Data
- Kids First Data Resource Center
- BioData Catalyst.

He also pointed out that the PTN will play a key role in coordinating upcoming COVID-19 responses. These efforts include supporting:

- RADx-RAD RFA: development of novel approaches to understand the spectrum of pediatric SARS-CoV-2 illness.
- RADx Underserved Populations (RADx-UP): understand the factors associated with disparities in COVID-19 mortality and morbidity.
- "Long COVID": NIAID-led workshop on Post-Acute Sequelae of COVID-19.

Dr. Hazra briefly described other examples of pivoting current NICHD-supported activities and funding for gestational research assessments for COVID-19:

- Maternal Fetal Medicine Unit (MFMU) Study
- Global Network: COVID-19 Infection Prevalence Data
- IMPAACT 2032: Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States.

Dr. Hazra closed by alerting participants to DASH as a centralized resource for researchers to share data from NICHD-funded studies. DASH also serves as a portal for requesting biospecimens from selected studies.

Introduction to Day 2 and Adjourn for the Day

Dr. Taylor-Zapata thanked presenters and other attendees for their participation in the Day 1 discussion and shared that she looked forward to continuing that dialogue on Day 2.

Day 2: Tuesday, December 15, 2020

Welcome/Recap of Day 1, Charge for Day 2

Perdita Taylor-Zapata, M.D.

Alison Cernich, Ph.D.
Deputy Director
NICHD, NIH

Dr. Taylor-Zapata began Day 2 with a brief recap of Day 1. Whereas Day 1 presentations provided detailed discussion of the role of the BPCA/PTN in pediatric drug development in specific studies. She emphasized that Day 2 discussion would address next steps and PTN's role in building and implementing a "big picture" approach to pediatric drug development.

Dr. Taylor-Zapata introduced **Dr. Cernich**, who discussed how implementing a framework with cross-cutting commonalities would advance the Institute's plans for future pediatric drug development efforts. Dr. Cernich recognized Dr. Taylor-Zapata as the "driving force" for many NICHD-sponsored initiatives, including the BPCA Program. Dr. Cernich thanked study investigators supporting BPCA for their incredible pivot in response to the COVID-19 pandemic, while at the same time continuing their "regular" work— meeting the ongoing challenge of developing programs that address the therapeutics and diagnostic devices that are unique to the NICHD population.

Dr. Cernich provided an update on the NICHD Strategic Plan 2020, summarizing the goals and core principles outlined in the Plan. As discussed in Day 1 presentations, the 2020 Strategic Plan defined three main goals:

- Identify where NICHD should take the lead
- Identify where NICHD should partner and collaborate
- Inform future investments in research, training, and infrastructure.

The Plan also specified overlapping core principles integral in meeting those goals:

- Transparency
- Evidence-based decisions
- Stakeholder participation.

Dr. Cernich described key milestones and timelines in the 2-year Strategic Plan development process, culminating in submission to the Council. She also discussed how the Strategic Plan goals and objectives apply to the BPCA Program, in particular, influencing and advancing NICHD research themes. Each of the five research themes has its own objectives. Dr. Cernich explained that the program is building a dashboard to monitor progress in meeting those objectives with the overarching goal of leading efforts to develop, test, and evaluate new and existing therapeutics and devices to find safe and effective solutions that meet the unique needs

of children, pregnant and lactating women, and people with intellectual and physical disabilities. She emphasized that it is impossible to address all five research themes simultaneously. It is necessary to prioritize based on scientific opportunity and resource availability. At the same time, the implementation process must be flexible to accommodate advances in technology and national health priorities, such as the COVID-19 pandemic. Dr. Cernich emphasized the importance of collaboration in implementing programs such as BPCA.

Dr. Cernich closed by summarizing next steps as NICHD moves forward in the strategic planning process:

- Continue refining the implementation process for Strategic Plan focus areas.
- Engage in new activities (and continue ongoing activities) to achieve the objectives and goals defined for each focus area.
- Develop metrics to track progress toward meeting Strategic Plan objectives.
- Report progress externally via an accessible web site (currently in development).

Reports from Breakout Sessions

Attendees next participated in roundtable discussions and breakout sessions that focused on a specific topic or issue. Groups then reconvened and reported out to all participants on issues, challenges, and opportunities that the small groups had discussed during the individual breakout sessions.

Systems Pharmacology
Jeremiah Momper, Pharm.D., Ph.D. and Gilbert Burckart, Pharm.D.

Dr. Momper noted that the Systems Pharmacology group discussed quantitative systems pharmacology (QSP) under the umbrella of computational and experimental methods to elucidate and apply pharmacologic concepts to the development and application of therapeutics. The group was mindful of the potential for overlap with other discussion groups, particularly the PK modeling group.

This group focused discussion on the need to better understand pediatric disease biology, looking at the ways that certain diseases differ in children versus adults. The group suggested that QSP models may be helpful in filling knowledge gaps that would facilitate extrapolation. Major aspects would include better understanding of disease physiology and progression between pediatric and adult populations. The group also discussed the potential application of QSP in understanding and predicting on-target and off-target drug safety in children.

Dr. Burckart then addressed ways the group thought these goals could be accomplished. This group also discussed the important issue of how to obtain sufficient resources.

The group included a representative from the FDA National Center for Toxicological Research (NCTR). NCTR frequently partners with academia, in terms of their animal models and as such, often looks to identify opportunities for further collaborations. The group also stressed the

importance of ensuring that these resources are available for investigators interested in conducting pediatric QSP.

Dr. Burckart noted that pharmaceutical companies tend to have a large number of modelers and system pharmacologists on staff. He suggested that there may be more opportunities to work with the pharmaceutical industry in a non-competitive space.

PK Modeling to Inform Dosing
Edmund Capparelli, Pharm.D. and Daniel Gonzalez, Pharm.D., Ph.D.

Dr. Gonzalez summarized the group discussion, which focused on the importance of educating clinical and scientific communities on progress made to date, particularly progress related to:

- Pediatric clinical pharmacology
- Importance of biologics
- PK/PD
- Dosing in the pediatric population
- Application of PK/PD modeling to characterize exposure response relationships, even for older off-patent therapeutics.

He noted the need to characterize PK/PD and pharmacogenomics of anti-cancer drugs, including identifying funding mechanisms for such studies and identifying opportunities to enhance collaboration between and NICHD/BPCA and European groups.

This group also discussed PK/PD pharmacogenomic studies of anti-cancer drugs. Specifically, the group stressed the importance of banking of pellets during bio-analysis to further encourage pharmacogenomic studies.

Dr. Capparelli stressed the need to identify gaps in knowledge for specific drugs to quickly determine what future studies are needed. He emphasized the importance of understanding the uncertainty and limitations of the various modeling approaches to determine when one can be used versus another. External model evaluation is needed to further assess published models and their appropriateness for use in dosing children.

This group also discussed the importance of:

- Obtaining guidance on systematic model development and evaluation, including best practices for communicating model results and reports, publications, and regulatory submission.
- Collecting genomic data and fostering collaborations to better understand the impact of genetic variation on PK/PD.
- Applying model-based approaches to characterize various factors that can contribute to ensure individual variability in pediatric populations. These factors include age, body size, disease states, concomitant medications, and genetic variation.

Pharmacoepidemiology
Jonathan Davis, M.D.

Dr. Davis noted that this group looked at pharmacotherapy of drugs for effectiveness, safety, and utilization of medicines. Group members recognized that there is an absence of comprehensive, high-quality, global pediatric databases that are interoperable and easily searchable with background complication rates. Without knowing what the background rate is, it is difficult to determine if something is a drug effect or an AE.

The group discussed EHR integration and looking at endpoints, recognizing the difficulty in differentiating drug-related effects in babies who may be receiving 30-40 different drugs.

The group noted that no existing databases have common data elements that everyone is using. Thus, investigators are currently unable to integrate these different databases in a way that makes sense.

Dr. Davis noted that an existing collaboration between the Critical Path Institute and FDA is trying to address this issue in neonate studies. The FDA has also funded an international neonatal consortium to build a large global database, compiling clinical trials data, EHR data, and other data from throughout the world in an attempt to answer some of these questions.

The group focused discussion on how pharmacoepidemiology can be used to advance research in "omics." The group discussed the following needs:

- Identify population subgroups that have a differential therapeutic response; establish effect estimates.
- Find the highest risk neonates (clinical/demographic) who might benefit the most from therapeutic intervention trials - link to genomic analyses.
- Document rare adverse reactions to drugs/emphasis on orphan drugs.
- Design and maintain pharmacogenomic databases.
- Study microbiome in relationship to drug effects.
- Address the importance of epigenetics.
- Involve key players— parents/patients, laboratorians, pharmacists, specialists, and geneticists.

The group emphasized that broad collaborative data collection and data harmonization will be integral to building this framework. There is also a need to create collaborative ecosystems among all children's hospitals. While considerable data exist, those data have not been linked to long-term outcomes.

Advancing Clinical Trials
Ed Connor, M.D. and Christoph Hornik, M.D., Ph.D.

This group organized their discussion into three topic areas:

- Overarching trial designs
- Trial endpoints and their relevance to the concept of extrapolation
- Trial recruitment and overall feasibility.

The group discussed types of overarching trial designs that could be used to account for longitudinal and developmental changes in endpoints. The group differentiated between the primary endpoint (a longitudinal outcome measure that changes over time) and a long-term safety issue that needs to be addressed during the trial.

Dr. Connor pointed out that discussion of advancing clinical trials is a broad and cross-cutting topic, one that includes all of the groups participating in this meeting. He suggested that proven "tools" are beginning to be utilized in pediatric clinical trials. At the same time, these tools present challenges. For example, the idea of changes over time in endpoints is one that was identified by investigators across several therapeutic areas in children. The group also stressed the critical need to find ways to better evaluate these types of endpoints.

Dr. Hornik underscored the importance of extrapolation, and the type of information clinical trials need to generate. For example, response to drug therapy and exposure-response relationships are key points to better inform and interpret study dynamics and outcomes.

The group discussed more systematic approaches to try to understand pediatric disease progression. Moreover, identifying similarity in the disease between adults and children will help lay the foundation for extrapolation. Ultimately, the response to a particular drug is the key sticking point when it comes to extrapolation.

The group examined the correlation between both short- and long-term outcomes as well as recruitment visibility. Participants also discussed difficulties in executing or operationalizing platform designs, while recognizing the value that they may bring and how they may increase visibility in particularly rare diseases.

Group members also described feasibility challenges arising as a result of COVID-19 such as reconciling telehealth needs and difficulties with e-consenting.

Pediatric-Friendly Formulations
Karen Thompson, Ph.D. and Susan McCune, M.D.

Dr. Thompson pointed out that this group included pharmacists, hospital pharmacists, and others who are actually administering these formulations to children in clinical settings.

She also noted that of the various pediatric populations, neonates represent the most challenging group. For example, determining the appropriate volume for administering into this population can be particularly complicated. There are issues with clogging of naso-gastric (NG) tubes due to volumes that are too large. In other instances, volumes are too small, or the neonate is too small.

Likewise, in preparing liquids for drug administration, hold times could range anywhere from 48 hours to 14 days depending on the actual drug. It is important to provide information on hold times in syringes before the drug is actually administered to the patient.

The group then discussed dosage forms. Group members noted that industry seems to be moving towards solid presentations of dosage forms for children because of stability advantages, mini tablets, or pellets administration. The group also explained that there are a number of challenges in administering mini tablets to neonates. Some pharmaceutical manufacturers are leaning towards direct administration on the tongue of infants, whereas others recommend mixing mini tablets with soft foods. Both approaches present further challenges as only certain foods can be mixed with the medicines due to pH sensitivities.

The group then discussed issues of palatability. In animal health therapy, there is clear guidance on what is considered acceptable; however, there is no such guidance for humans. In humans, palatability is assessed on a hedonistic scale (liking versus disliking). By and large, children prefer flavored medications. A second palatability issue is texture, which impacts swallowing ability and can be modulated with viscosity effects.

The group next discussed engagement of patients in their care. It was noted that some current "apps" encourage children to take ownership of their health. These apps acknowledge that children can be engaged in different ways that actually can help with adherence for chronic treatments.

This group was perhaps the first time where formulators, clinicians, and pharmacists were together to discuss delivery of pediatric formulations. They agreed that such a forum, with real-time feedback on the current process, can have real impact on how to make improvements. Group members suggested taking this discussion further and continuing this forum beyond the current meeting.

Dr. McCune reminded the group of the importance of including the voice of the patient and the parent(s), especially given the useful data from apps (discussed above) that might be leveraged. She agreed that a collaborative effort of formulators, industry pharmacists, and clinicians, as well as patients and parents could be especially useful. Combining PTN efforts with the IQ Consortium and adding some additional stakeholders could prove especially helpful in developing experience-based platforms associated with acceptable whole foods that can be mixed with some of these dosage forms.

Biomarkers Research
Greg Kearns, Pharm.D., Ph.D.

Members of this group agreed that biomarkers need to be practical, predictive, purpose-appropriate, and potentially valuable. **Dr. Kearns** noted that while there is considerable information and a lot of promise on imaging studies, significant challenges remain in the practicality of using some of these biomarkers.

He emphasized the need to look at what can be accomplished within the context of a clinical trial. Specifically, the group discussed challenges unique to studies of neonates due to their small physical size. Moreover, neonatal populations relative to other populations and drug studies are small. Additionally, the group agreed that the large amount of variability leads to additional challenges.

The group also acknowledged challenges related to diverse populations. The group discussed race versus ethnicity versus ancestry and how and when these categorizations need to be used. In some cases, these categories may prove useful in identifying an important biological difference. In many cases, however, there is no impact. The group agreed that social constructs are important as they can impact biology, but study developers need to be mindful of and understand how to incorporate that information into clinical trials.

In discussing how to separate patients who will respond versus not respond to a therapy, Dr. Kearns suggested that a more informative approach to conducting a clinical trial might be to look at people on the "ends," rather than those in the middle. This approach could be more informative than other methods used in the past.

The group also discussed the potential usefulness and value of artificial intelligence and machine learning to look at multifaceted biologic responses to treatments that change over time. The group cited the example of accessing EHRs and being able to change information into data and using those data within the context of assessing drug response.

The group also discussed the role of PK and PD in development, acknowledging the significant deficiencies that still exist in PD development. There are not yet any great approaches to be able to map the impact of ontogeny on drug PD. The only way to make this happen is to utilize the appropriate biomarkers that can be used as surrogates of drug effect. The group pointed out that general agreement among the scientific community, regulatory community, and from within NICHD will provide the impetus to push ahead.

Using real-world data will help move from biologic plausibility of a biomarker to proof of concept and then proof of utility. The group underscored that NICHD has a key role in transitioning from proof of concept to proof of utility.

Dr. Taylor-Zapata thanked group leaders and moved to the Question and Answers portion of the meeting.

Questions/ Comments for Breakout Session Group Leaders

Question: What can be done to increase diversity among study participants? For example, has there been discussion regarding increasing diversity among study developers and among those who conduct those studies?
Answer: Dr. Taylor-Zapata pointed out that within the PTN, there has been an effort to collect data on diversity from the very beginning of the study design through the protocol development process. Also, there have been concerted efforts to continually reevaluate diversity once a study is implemented. **Dr. Zimmerman** noted that based on information collected to date, efforts to address and maintain diversity in PTN studies have been successful. However, isolating specific factors that advance diversity are less clear. She emphasized the necessity for including diversity in studies as part of a nationwide conversation.

Dr. Hornik noted that the issue of diversity was raised during survey responses to clinical study areas. He suggested that part of the solution should focus on involving site investigators and site research staff. These individuals bring a broader overarching understanding of the factors that would influence diversity within a specific study. Dr. Hornik also noted that the complexity and differences from one NICHD study site to another are significant. Study developers would benefit from working with site principal investigators who understand the dynamics influencing diversity underlying design and conduct of a specific study. He also emphasized that this information may not be generalizable, but it is still valuable.

Dr. Pawlyk noted that NIH has undertaken significant initiatives to enhance diversity in human subject studies, especially in clinical trials. These efforts address diversity among typically underrepresented groups, based on ethnicity, race, and rural distribution. The issue of workforce diversity has also been getting more attention among NIH components, especially NICHD.

Dr. Capparelli focused on the need to think about ways to foster broader training elements in initiatives such as the T32 program. He also encouraged participants to identify ways to partner with other groups within NIH. There is a growing need to involve pediatric reviewers from outside NICHD who understand the issues impacting pediatric clinical study development and implementation.

Wrap Up, Next Steps, and Closing Remarks

Dr. Taylor-Zapata introduced **Mark Turner, Ph.D., MBChB**. Dr. Taylor-Zapata explained that she and Dr. Turner have been working together to develop a generic framework that stakeholders could work from to provide an overall structure to enable pediatric drug development studies. Dr. Turner pointed out that these studies often address cross-cutting common themes.

Dr. Taylor-Zapata invited participants to become actively involved in the next steps in developing this framework. She solicited their input regarding identifying gaps, as well as resources. Dr. Taylor-Zapata also asked them for a 4-hour commitment during 2021 to engage in focus group discussions for framework document development. Some participants may be asked

to serve as subject matter experts to structure and assess success in defining and reaching the goals of the draft framework:

- Need to alert, centralize, and effectively advertise to contributors the large amount of sound and proven practice tools and resources that currently exist in pediatric drug development.
- Identify and address remaining gaps in good practice.
- Promote integration between stakeholders engaged in various stages of drug development.
- Integrate approaches such as big data, real-world evidence, and use of medical technology in drug development.

Dr. Taylor-Zapata concluded by thanking attendees for their participation, urging them to continue engaging in the framework development process, and in taking advantage of existing online resources through the NICHD such as DASH, the BPCA website, and information on the Pediatric Trials Network website.