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

2021 Best Pharmaceuticals for Children Act (BPCA) Stakeholders Meeting

December 2-3, 2021

Meeting Summary

Purpose: The purpose of this meeting was to provide updates on (1) the Best Pharmaceuticals for Children Act (BPCA) Clinical Program at the National Institutes of Health (NIH) and (2) the development of the BPCA Framework to Enable Pediatric Drug Development.

Day 1: Thursday, December 2, 2021

Welcome 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, NIH

Dr. Taylor-Zapata opened the meeting and welcomed participants. She outlined the goals for the meeting: to provide updates on the BPCA Clinical Program, including the prioritization process and the Pediatric Trials Network; to provide an update on the BPCA Framework to Enable Pediatric Drug Development Initiative, including a forum for the exchange of ideas through roundtable discussions and brainstorming sessions.

Dr. Pawlyk thanked participants for attending the meeting and their work with the BPCA Program. He noted that we are all at the meeting to address a central problem: that physicians and patients must often make decisions on medication and vaccine use with limited data on rigorously conducted regulatory studies as well as limited approval of medications for a population. Up to 59% of the U.S. population is made up of people who typically are not included in research studies, such as pregnant women, children, older people, and individuals with intellectual and physical disabilities. Recently, the NICHD developed a five-year strategic plan with five scientific themes. One of these themes is to advance safe and effective therapeutics and devices for pregnant and lactating women, children, and people with disabilities. The plan also includes aspirational goals such as facilitating the application of precision medicine and training the next generation of scientists. Dr. Pawlyk gave an overview of the Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB), whose mission addresses the health of the aforementioned underrepresented groups.

BPCA Program Updates and Overview of the BPCA Framework to Enable Pediatric Drug Development Initiative
Perdita Taylor-Zapata, M.D.

Dr. Taylor-Zapata shared updates from the BPCA Program and gave an overview of the BPCA Framework to Enable Pediatric Drug Development. BPCA, which was implemented in 2002, gives pharmaceutical companies six months of exclusivity to conduct pediatric clinical trials. Under the BPCA Program NICHD's key responsibilities include:

- Prioritizing needs in pediatric therapeutics.
- Conducting clinical trials in pediatric therapeutics via the Pediatric Trials Network.
- Submitting trial results to the U.S. Drug and Food Administration (FDA) for labeling changes.
- Updating labels with important information from the BPCA sponsored studies.
- Facilitating pediatric pharmacology training and translational research.
- Disseminating data to researchers and patients.

To date, the NIH BPCA Program has prioritized 220 drugs across 50 specific therapeutic areas. Approximately 47 clinical trials have been conducted, with 30 clinical study reports submitted, 15 pediatric label changes, and 100 publications. As the program has matured, its parameters, potential, and expertise have become clearer. One of its newest efforts is the Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub, which is focused on bridging the gap between translational and clinical research in pediatrics and maternal health.

Over the past year, the BPCA program has sponsored the development of a pharmacology resource guide called the Framework to Enable Pediatric Drug Development. The goal was to develop an annotated, curated collection of resources to assist drug developers, researchers, and clinicians while simultaneously identifying pathways to close remaining gaps in good practice. Long-term goals for the framework are to bring guidelines together and foster more team science in pediatric drug development. The program identified stakeholders who could benefit from and contribute to framework development, including clinical and preclinical investigators, regulators, patients and patient advocates, and industry, and invited them to participate in pediatric assembly working group discussions. Over 400 participants attended at least one call, with 184 active participants and an average of around 40 participants per assembly. Discussion points for these assemblies included documents and guidelines about good practice, which documents should be read first and could unlock the field for people who were not familiar, and consensus statements that need to be centralized. The program also set parameters for identifying resources. As of August 25, 2021 over 200 resources were received and these were scored, sorted, and adjudicated by assembly members via a voting and curation process. Those resources in the public domain could be given classifications such as Read First or Helpful Explanation, whereas non-public resources would be classified as Additional Resources. Assembly participants identified two articles in particular that would qualify as Read

First papers except they were not publicly available. Publishers and investigators were contacted and a case was made for their importance in being part of the framework. As a result, publishers agreed to move these two papers to the public domain.

BPCA Framework Outcomes and Gaps

Advancing Clinical Trial Design
Ed Connor, M.D.
Institute for Advanced Clinical Trials for Children (I-ACT)

Christoph Hornik, M.D., Ph.D.
Duke Clinical Research Institute

Dr. Hornik reported that the Clinical Trials Assembly included 76 active members, with approximately 50% from industry and consulting backgrounds and the rest from government, regulatory, academia, and other groups. The group was highly active and provided a total of 72 resources, 42 of which were selected for inclusion in the framework. These resources were varied in terms of the specific issues addressed: five were considered "Read This First" to provide introductory guidance, nine were considered helpful on a more general basis, 14 were considered helpful on specific topics and situations, and 14 were considered helpful additional resources. The assembly identified several gaps, including digital endpoints in clinical trials; digital tools to capture patient-reported outcomes; remote, decentralized, or hybrid clinical trials; and platform trials in pediatrics. **Dr. Connor** added that the clinical trials topic cuts across many of the other groups and stated that clinical trial innovation and design represents the path forward for pediatric drug development.

Pharmacodynamic Biomarkers
Gregory Kearns, Pharm.D., Ph.D.
Texas Christian University

Dr. Kearns noted that throughout the last 30 years the amount of pharmacokinetic (PK) data generated in infants, children, and adolescents has greatly increased. In 2019, Professor Nick Holford commented that PK studies should not be conducted without pharmacodynamic (PD) endpoints. The Pharmacodynamic Biomarkers Assembly members embraced that message in its work to identify biomarkers that can be used as PD endpoints. The assembly had 26 active members, with 38% from government, 27% each from academia and industry, and 8% from other groups. The Assembly received 23 resources for consideration and elected to include 14, with 6 considered "Read This First" and 8 considered helpful. The Assembly identified gaps, including the need for available and validated biomarkers for pediatric research and clinical trials and criteria for selection of optimal biomarkers in pediatric clinical trials. Specific challenges to develop biomarkers for children include the lack of validated endpoints in children, the need to avoid invasive and repeated sampling, and the potential impact of development.

Pediatric-Friendly Formulations
Karen Thompson, Ph.D.
Merck

Dr. Thompson reported that the Pediatric-Friendly Formulations Assembly included 47 active contributors, with 49% from industry/consulting, 28% from academic/research, 13% from government/regulatory, 6% from other groups, and 4% from non-profits. They received 74 resources total and selected 20 resources for inclusion in the framework, including guidance documents from the FDA and other regulatory bodies. Identified gaps included the applicability of the Biopharmaceutical Classification System (BCS) to pediatrics and extrapolation for efficacy and safety, the ontogeny of some enzyme systems, and the lack of understanding around the developmental status of organ systems, metabolism, and absorption in young children, particularly neonates.

Pediatric Pharmacoepidemiology
Jonathan Davis, M.D.
Tufts University

Dr. Davis noted that this is a unique opportunity to look at drug use in large populations of children. This assembly had 16 active participants, with 38% from academia/research, 31% from government/regulatory, 19% from other groups, and 13% from industry/consulting. Out of the 36 resources the group reviewed they selected 25 for inclusion, with four considered "Read This First," 11 that were helpful, and 10 additional resources. The assembly identified four major gaps: a lack of patients to conduct randomized controlled trials in children for drugs of interest; the absence of high-quality, high volume, easily searchable pediatric databases; the need for an improved focus on necessary endpoints; and electronic medical record integration with lab results, clinical data, medication administration, and pharmacy records.

PK Modeling to Inform Dosing
Edmund Capparelli, Pharm.D.
University of California, San Diego

Dr. Capparelli reported that the PK Modeling Assembly had 46 active members, with 37% from industry/consulting, 30% from academia/research, 22% from government/regulatory, 7% from other groups, and 4% from non-profit groups. They received 20 resources and included 13 in the framework, five of which were considered "Read This First," five were helpful explanations, and three were additional resources. The Assembly identified an overarching need for communication and recognized that much of the information that has come forward in the last 20 years has focused more on drug development than clinical use. With these elements in mind, they identified the following gaps: a need to leverage data to assess the predictive performance of a model once it's published; the need for integration of pharmacogenetics (PGx) into PK/PD models to account for the role of genetic variation; and the need for dose optimization that is specific to the pediatric population.

Systems Pharmacology
Gilbert Burckart, Pharm.D.
U.S. Food and Drug Administration

Jeremiah Momper, Pharm.D., Ph.D.
University of California, San Diego

Dr. Momper noted that the term quantitative systems pharmacology (QSP) refers to dynamic interactions between drugs and biological systems with an overarching objective of predicting pharmacodynamic effects within the system. While there is strong consensus that QSP could be impactful for pediatric drug development, that potential has not been fully realized. The Systems Pharmacology Assembly consisted of 25 active participants, with 40% from industry/consulting, 32% from government/regulatory, 24% from academia/research, and 4% from unknown groups. They received 22 resources and included 17 in their final list, including 6 that were considered "Read This First," six that were considered helpful, and five additional resources. The assembly identified the following gaps and challenges, using a landmark NIH white paper as a launching pad: characterizing quantitatively the biochemistry of drug targets and associated networks across the pediatric age continuum; exploiting diverse and multi-omics data to create PD biomarkers that inform integrated, multi-scale models of drug response in children; conducting failure analysis as a means to understand why products fail in pediatric clinical trials and how such failures might be avoided in the future; developing and supporting information exchanges for pediatric QSP, particularly related to clinical data and electronic medical records; and the fact that widespread adoption of QSP in pediatric drug development is limited by a shortage of appropriately trained QSP scientists. **Dr. Burckart** added that, as of November 2021, there have been 213 submissions to the FDA related to QSP.

Questions and Answers/Next Steps
Perdita Taylor-Zapata, M.D.

Dr. Taylor-Zapata presented the next steps for the framework. NICHD is working to finalize the framework document, with the goal of making it a publicly-available, web-based resource. In addition to the BPCA website, the program team is looking for additional homes for the framework to make it a more global resource. Once this has been secured, the program will develop a curation plan that will be integrated into the prioritization process. The draft resource document has been sent to the internal trans-NICHD governance committee for review; final recommendations will be submitted to NIH-wide committees, such as NIH-wide BPCA Liaisons, by early 2022. Dr. Taylor-Zapata presented a sample schematic diagram for the framework and invited participants to reach out with ideas and suggestions for future platforms.

Pediatric Drug Development Roundtable Gap Discussion
Moderator: Mark Turner, MBChB, Ph.D.
Professor of Neonatology and Research Delivery
University of Liverpool

Stephen Balevic, M.D.
Duke Clinical Research Institute

Gilbert Burckart, Pharm.D.
FDA

Edmund Capparelli, Pharm.D.
UCSD

Ed Connor, M.D.
I-ACT

Jonathan Davis, M.D.
Tufts University

Karen Thompson, Ph.D.
Merck

Christoph Hornik, M.D., Ph.D.
Duke Clinical Research Institute

Gregory Kearns, Pharm.D., Ph.D.
Texas Christian University

Thomas Miller, Ph.D.
Bayer

Jeremiah Momper, Pharm.D., Ph.D.
UCSD

Aaron Pawlyk, Ph.D.
NIH

Gerri Baer, M.D.
FDA

Dr. Taylor-Zapata introduced the session and invited participants to discuss the ecosystem of pediatric drug development, what can be done to move the field forward, and how to bring children to the forefront during the early stages of scientific advances. **Dr. Turner** invited the assembly leaders and expert contributors to discuss existing gaps and possible solutions.

Biomarkers: Dr. Kearns identified a gap between the identification of a functional biomarker which links drug exposure and response and the FDA's acceptance of the inclusion of such a biomarker into the Phase 2 program for development of a drug for pediatric patients. He proposed encouraging industry to use existing data regarding drug mechanism of action and identify suitable candidate biomarkers that could be used to design a PK/PD trial, and reconsidering the current strict definition of "validation" and associated requirements to enable innovation. Dr. Turner suggested that there might be a need for better academic practice when using functional biomarkers. **Dr. Baer** said that when promising biomarkers exist it is necessary to have trials that incorporate both the biomarker and the long-term clinical gold standard to compare their performance. Dr. Burckart added that FDA has a Biomarker Qualification Program which has been underutilized, and that in the regulatory context "validation" and "qualification" are two very different things. The use of primary endpoints in clinical trials has evolved, and those endpoints are not always the best indicators for long-term clinical outcomes. **Dr. Miller** said that this topic was top of mind for industry and that from his perspective it's important to consider the intended goal for the biomarker, i.e., assessing target engagement or using the biomarker as a surrogate to pursue registration, and it is important to consider this early on in the development process. Dr. Pawlyk noted that The Foundation for the NIH (FNIH) has a Biomarkers Consortium, which is a collaborative effort between the FDA, the NIH, FNIH, and various industry partners. Partnerships like the Consortium can provide a space for multiple companies to work together and support the development, validation, and qualification of a biomarker that can be used by multiple companies. He suggested that there could be

biomarkers and disease indications that garner enough interest to be put forward for consideration in that forum.

Dr. Balevic said that linking biomarkers to clinical outcomes has been challenging and noted that biomarkers also play into parallel conversations about appropriate outcomes in pediatric drug trials, such as patient-reported outcomes. He also encouraged the community to think about the potential use of biomarkers to support PK/PD modeling and extrapolation pathways and how to leverage what is known about biomarkers in adults from the literature. Dr. Hornik said that increasing the knowledge of effect biomarkers is akin to increasing knowledge of PK, and that incentives could be created to ensure that PK studies are never conducted without effect biomarkers. Given the number of successful PK studies that are conducted, this could increase knowledge of effect biomarkers, and the recognition of an effect biomarker role might help narrow down the biomarkers to pursue for correlation with clinical efficacy.

Clinical Trials: Drs. Hornik and Connor identified a gap around the design, implementation, and quality of digital tools that are used to electronically capture patient-reported outcomes. One possible solution is to include digital biomarkers in current biomarker development efforts in children. They also suggested including digital data collection methods paired with traditional data collection methods in earlier phase trials to help validation, and to include children as appropriate in adult digital device validation studies. Dr. Balevic noted that decentralized virtual trials are becoming more common, especially during the COVID-19 pandemic. Digital data is still somewhat of a black box and it is important to think about how to use patient-reported outcomes as an outcome measure. Dr. Pawlyk suggested that point of care diagnostics could be a device space to link biomarkers to a harder clinical outcome, especially in a digital environment where the data is more easily combined. Dr. Miller said that if data can be captured remotely in a reliable way, everyone will benefit, including the children, their caretakers, and the individuals responsible for the trial. Regarding digital biomarkers, validation by age strata within children will be important as well. Dr. Miller also noted that life science companies that focus on medications are typically not the creators of digital devices; the medical technology industry drives innovation in that field, and he suggested that they should be included in this conversation. He also suggested that a prioritization approach could be applied to an array of biomarkers similar to the approach that exists for drugs, and connections could be made with public-private partnerships already interested in this topic.

Dr. Philip Walson agreed that devices are often accepted as diagnostic tools by the FDA but are not used for trials because the FDA separates devices from drug products. Dr. Burckart said that there are co-development programs where a device is developed along with a drug, but those are sponsor-driven. Dr. Baer said that when attempting to change labeling or garner an approval, the most important thing to do is put the information out there, bring it to the FDA, and listen for feedback. With regard to patient-reported outcomes (PROs), the low-hanging fruit might be converting existing PROs into electronic form so that they are easier to administer. Dr. Balevic talked about the use of digital technologies to support decentralized trials, which offer the opportunity to enroll more patients and more representative patients. This could be especially important for the rare disease population.

Formulations: Dr. Thompson identified a gap in the area of pediatric-friendly formulations. Current references suggest that there is not a direct application using the biopharmaceutical classification system (BCS) to extend to children, partly due to the lack of knowledge of GI ontogeny to influence BCS models. The proposed solution involves data mining; researchers are generating large amounts of data and information about PK in adults and children, and that data needs to be collected and shared to seek to further understand BCS and its application in children. Dr. Turner noted that before data can be mined it must be warehoused, and there are challenges with making sure it is interoperable and annotated appropriately to allow mining. Dr. Taylor-Zapata said that one of the components of the MPRINT Hub (https://www.nichd.nih.gov/about/org/der/branches/opptb/mprint) is to serve as a knowledge portal for this type of data. **Dr. Sara Quinney** added that the Hub is attempting to create a database for maternal and pediatric populations that can be mined, and they plan to develop PBPK models to look at the ontogeny of enzymes and inform models for extrapolation to children.

Dr. Miller said that he was glad to hear ontogeny mentioned in the context of enzymes, and that receptor-based ontogeny is a similar dynamic with equal relevance. The literature is scant on this topic, and he suggested that this could be companion information in a repository. Dr. Baer said that data sharing and borrowing is the way to go, and it's something the FDA is very familiar with because pediatrics does not have a large body of data on ontogeny or PK. One of the most challenging areas is excipients and toxicokinetics, particularly in neonates, and any shared resources would be helpful from a regulatory perspective. Dr. Turner mentioned the STEP database (http://www.eupfi.org/step-database-info/), which is a database of excipient characteristics maintained by the European Paediatric Formulation Initiative (EuPFI). Dr. Thompson said that the problem with excipient data is that excipients are studied in the context of a formulation, not in a vacuum. Dr. Burckart added that there is a lot of proprietary information in pediatric studies and suggested that they think about ways that sponsors can be encouraged to share that information and make it more readily available. Dr. Momper said that the proprietary information could be de-identified to some degree when looking at issues around the BCS, and some questions could be answered without identifying sponsors or drugs to put forward broad recommendations.

Pharmacoepidemiology: Dr. Davis identified a gap in the area of pharmacoepidemiology: there are insufficient numbers of children to conduct all of the clinical trials that need to be completed, and this is especially true for rare diseases and trials where adults are studied first and children are included last with ages slowly being reduced. Proposed solutions are to include parents earlier in the drug development process, build trust with communities, especially those with underrepresented minority populations, and conduct global studies. Dr. Balevic added that it was important to include the patients themselves and disease advocacy organizations as stakeholders. Dr. Turner said that enrolling children in follow-up and observational studies for drug safety could be a way to improve information about medicines within specific investigational paradigms, as well as using registries. Dr. Baer added that drug safety can be connected to digital tools such as the V-safe program.

Dr. Davis asked whether panel members thought that it was a good idea to slowly reduce ages in a trial or if there were opportunities to study small numbers of adults for safety and then move more quickly into children. Dr. Miller said that his company is trying to push the initiation of pediatric development earlier, but for most of their studies they start with older children and then do a cohort walk back with Data and Safety Monitoring Board (DSMB) reviews in between. He added that disease advocacy groups are an important force for getting trials enrolled. Dr. Momper said that some institutional review boards (IRBs) have research participant advocacy programs which serve as neutral parties and meet with potential research participants to address concerns. While that has not been geared towards pediatric populations in the past, it could be an opportunity to leverage.

Dr. Connor said that including underrepresented minorities in clinical trials is a key issue and diversity, equity and inclusion efforts have demonstrated that care and research are more accepted and better done when the investigators and staff are members of that community. Dr. Burckart said that for every pediatric study plan, the FDA's Pediatric Review Committee (PeRC) discusses the issue of including younger children as quickly as possible. Dr. Hornik said that there is still a lot to learn about the timing and continuation of engagement with the families of pediatric trial participants. Dr. Pawlyk said that even when there is a clear regulatory path and patients and families are willing to participate in studies, IRBs and general clinical trialists are still reluctant to include pediatrics, and this is another gap to address.

PK Modeling: Dr. Capparelli identified a gap around the integration of PGx into PK/PD models to account for the role of genetic variation. Proposed solutions are: to include metabolite and biomarker measurements in pediatric trials; leverage existing adult PG and PK/PD models into more mechanistic models combining adult and pediatric data that account for cofounders of size, PG, age, formulation and co-morbidities; and use allometric scaling, PBPK and population PK models for simulation and qualification of existing PK/PG models and assessment of PG driven pediatric dosing. Dr. Kearns said that the issue of metabolite profiles is very important, especially in young babies, because a genotype can only predict clearance when there is concordance between the genotype and the phenotype and adult levels of activity for a given enzyme are reached. Dr. Pawlyk added that one of the MPRINT Hub centers at Vanderbilt Medical Center is focused on pharmacogenomics.

Dr. Miller noted cross-linking between the different topics and noted that decentralized clinical trials, which limit the number of live study visits, might not allow enough sampling to adequately assess the metabolic fate of the medicines. He asked whether translational non-human models could provide any perspective on this topic. Dr. Kearns said that the overall utility of animal models for developmental studies of drug metabolism is limited, but for studies of drugs that are non-extensively metabolized, pigs are excellent models. Dr. Balevic said that he had observed several common themes across the gaps, including the need for more PK/PD studies, integrating pharmacogenomics, and enrolling diverse clinical trial populations, which then ties into pharmacoepidemiology solutions and decentralized trials.

<u>Quantitative Systems Pharmacology</u>: Drs. Momper and Burckart identified one gap for quantitative systems pharmacology, with possible implications for the former topics: widespread adoption of QSP in pediatric drug development is limited by a shortage of appropriately trained QSP scientists. In order to close this gap, they proposed that NICHD should encourage and support pre- and post-doctoral training programs in QSP, along with partnerships, resources and expertise from the pharmaceutical industry, academic, and nonprofit organizations. Dr. Burckart added that the FDA has a large number of PharmD students who request FDA rotation and are interested in drug development, and there is a shortfall in training programs for graduates interested in QSP. Dr. Baer asked if there was enough of a demand from pharmacy students for schools to increase the number of trainees they can accommodate. Dr. Burckart said that PharmD training has greatly expanded in the last 15 years, and there are schools that recruit pharmacy students who are not interested in traditional pharmacy. There are residencies available, but there are only enough spots for about half of the students who apply every year.

Dr. Balevic said that many pediatricians and pediatric clinical researchers are not taught the fundamentals of clinical pharmacology and there is a major need in this area. He spoke about his experience working with the NICHD T32 program and said that the proposed solution for more NICHD training programs in QSP was important. Dr. Burckart asked if the T32 program could be expanded. Dr. Pawlyk said that NICHD was thinking about ways to leverage the T mechanisms, individual F awards, and the K career faculty awards and he asked for participants' thoughts about how to leverage the pharmaceutical sector for training opportunities and information. He added that NICHD encouraged people to submit applications to the parent T32 announcement, and if individuals have a particular area that they would like to build the T32 program along the Institute would be interested in discussing those opportunities.

Dr. Miller said that he joined the industry as a fellow, and he has noticed over his career that that pathway has become more commonplace. He said that it would be good to get a sense of how many fellowship programs exist and suggested partnering with organizations like the Pediatric Pharmacy Advocacy Group. Dr. Thompson said that joint fellowships with surrounding universities could feed into the pipeline to have access to expertise, and this could be done in a public-private partnership format. Dr. Turner suggested that a working group could move that forward. Dr. Pawlyk asked if QSP in general was advancing quickly enough and pediatrics was lagging, or whether a broader effort was needed around QSP training. Dr. Burckart said that it was in the pediatric realm and an emphasis in QSP would be an advantage to pediatric patients. Dr. Turner asked if there was willingness for continued discussion on how to move the education and training agenda forward, and who would convene it. Dr. Taylor-Zapata said that the BPCA program has a primary role in making sure that the conversation continues, but the implementation will require significant collaboration.

Summary, Introduction to Day 2 and Adjourn for the Day
Perdita Taylor-Zapata, M.D.

Dr. Taylor-Zapata reiterated the theme of collaboration and common threads and said that she heard a sense of hope and forward movement during the day's discussion. She thanked the participants and outlined the agenda for Day 2.

Day 2: Friday, December 3, 2021

Welcome
Perdita Taylor-Zapata, M.D.

Dr. Taylor-Zapata welcomed participants back for Day 2 of the meeting and outlined the agenda.

NICHD Update – COVID Response
Robert Tamburro, M.D.
Program Officer, Pediatric Trauma and Critical Illness Branch
NICHD, NIH

Dr. Tamburro discussed NIH's COVID-related pediatric research, including the MIS-C and PreVAIL kIds cohorts, the Safe Return to School Diagnostic Testing Initiative, the Pediatric COVID-19 Dashboard, and the RECOVER Initiative. The Collaboration to Assess Risk and Identify loNG-term outcomes for Children with COVID (CARING for Children with COVID) program was formed to better understand SARS-CoV-2 in children, including multi-system inflammatory syndrome in children (MIS-C). This trans-NIH program leverages the clinical networks of the NICHD, the NHLBI, and NIAID to research SARS-CoV-2 in children by designing and supporting studies such as MUSIC, PRISM, POPS02, and PreVAIL kIds.

The MUSIC project is an observational study with 1,074 children with MIS-C enrolled at 33 sites across the United States, designed for five years of follow-up. The primary focus of the study is left ventricular dysfunction and the development of coronary artery aneurysms, and it also assesses other organ dysfunction, inflammation, and major medical events. The PRISM observational study has enrolled approximately 235 children, including 123 with MIS-C, at 20 sites across the country. The study focuses on inflammatory pathways associated with MIS-C and pediatric COVID and has a six-month follow-up plan. POPS02 is a PK study of medications used to treat COVID in children. It has enrolled 460 cases of pediatric COVID and 120 MIS-C cases at 34 sites. Over 100 children treated with remdesivir have been enrolled, including 40% that are less than 12 years old, with PK data pending. Data on the first 57 MIS-C patients has been submitted to the Kids First Data Resource Portal. The MUSIC, PRISM, and POPS02 studies account for over 20% of all documented cases of MIS-C in the U.S., and data from all three will be made widely available to facilitate further research.

Predicting Viral-Associated Inflammatory disease severity in children with Laboratory diagnostics and artificial Intelligence (PreVAIL kIds) is part of both CARING for Children with COVID and the RADx Radical Initiative. PreVAIL kIds is developing multimodal biomarker signatures, leveraging artificial intelligence and machine learning to develop translational tools to understand the spectrum of pediatric COVID, rapidly diagnose and characterize MIS-C, and predict the longitudinal risk of disease severity. $20 million has been allotted to eight research teams with multidisciplinary expertise. The program's 75 sites span 30 U.S. states, with international collaborations in the United Kingdom, Canada, Asia, Africa, and South America. The goal is to enroll 60,000 children with racial and ethnic diversity using prospective and retrospective accrual and leveraging biorepositories. Enrollments are ahead of projections and have exceeded goal accruals, with over 4,500 prospective and 33,000 retrospective participants enrolled to date. The program is informing care with 30 publications and 6 national publications, including a recent feature article in the *Journal of Clinical Investigation*.

The Safe Return to School Diagnostic Testing Initiative is a component of the RADx Underserved Populations (RADx-UP) Program. In April of 2021 NIH announced that it would award over $33 million to fund projects at ten institutions to build evidence around safely returning students, teachers, and support staff to in-person school in underserved and vulnerable communities. In July of 2021 the NIH made a second set of awards across five states totaling $15 million to ensure geographic distribution and overall diversity. The program had its first workshop in August of 2021, with presentations by the funded investigators. Preliminary results indicate that COVID-19 testing is feasible and acceptable in schools across a range of populations and settings. Following implementation of testing programs after COVID exposure, there was an increase in access to testing and a decrease in the number of days in quarantine for students and staff. With testing and mitigation strategies in place, low rates of within-school transmission were observed, although this data was gathered before the Delta variant became dominant. Researchers noted that both surveillance and post-exposure testing are important strategies to return and keep students in school, especially for those children who may not be able to effectively use other mitigation methods.

The Pediatric COVID-19 Severity Dashboard is an interactive dashboard for near-real-time tracking. It will be updated approximately weekly and will analyze the trajectories of pediatric COVID hospitalization rates, and it will leverage the National COVID Cohort Collaborative (N3C), which aggregates electronic health record data from more than 50 pediatric centers. The REsearching COVid to Enhance Recovery (RECOVER) program studies the long-term effects of COVID-19. It is a trans-NIH effort to improve the understanding of and develop strategies to prevent and treat post-acute manifestations of COVID infection across the lifespan, including children.

Advancing Pediatric Therapeutics: Regulatory Perspective
Lily Mulugeta, Pharm.D.
Clinical Analyst, Office of Clinical Pharmacology
Division of Pediatric and Maternal Health, FDA

Dr. Mulugeta spoke about the efforts of her agency and division to advance pediatric therapeutics and drug development. Over the past few years, the FDA has used multiple methods to advance PDD, including leveraging outcomes of regulatory science research and using stakeholder engagement efforts to inform policy. Dr. Mulugeta presented several examples of regulatory research projects led by the Division of Pediatric and Maternal Health that focused on partial-onset seizures, schizophrenia/bipolar I disorder, pediatric heart failure, and hypertension. All four used systematic reviews of adult and pediatric data to support extrapolation and had major impacts on policy. Another ongoing project seeks to understand the high number of negative or failed trials in pediatric major depressive disorder (MDD) and the variation in drug response between adult and pediatric patients. Dr. Mulugeta also gave examples of the FDA's engagement with scientific and clinical experts and stakeholders through public workshops. These workshops have focused on topics such as pediatric heart failure, pediatric inflammatory bowel disease, polyarticular juvenile idiopathic arthritis, and acute pain in patients less than 2 years old.

In August of 2021 the FDA's Division of Pediatric and Maternal Health conducted a crowdsourcing challenge in an effort to obtain more input from external stakeholders on research questions that can be addressed by analysis of pediatric and adult clinical trial data submitted to the FDA. The Division reached out to scientists in academia, industry, and other regulatory agencies through multiple promotion channels. They received 74 submissions, with 20% of submitters identifying as clinical researchers. Of those who identified as clinical researchers, 80% identified as being from industry. Approximately 60% of the submitted research questions came from industry, with 14% from academia, 5% government (including FDA, NIH and others), and 2% from patient advocates. The submissions spanned many categories of research questions, including: the use of biomarkers for pediatric-specific diseases, as well as bridging biomarkers for rare diseases; safety and efficacy data; the use of external data and historical placebo data; diversity, inclusion, and global alignment; drug formulation; oncology; and the extrapolation of PK/PD data and dose selection. The FDA hopes to conduct several similar challenges in the future. Dr. Mulugeta said that from her perspective, the next frontier in advancing PDD will be tackling challenges with formulation development, increasing the efficiency of clinical trial operations, developing biomarkers and registries in a pre-competitive space, and the broader application of innovative approaches such as bridging biomarkers and Bayesian approaches.

Accomplishments and Challenges in Pediatric Drug Development: Experience of the Pediatric Trials Network

Rachel G. Greenberg, M.D., M.B., M.H.S.
Duke University Medical Center
Duke Clinical Research Institute

Dr. Greenberg gave a presentation on the Pediatric Trials Network (PTN) and its accomplishments and challenges. Only a small percentage of drugs and devices approved by the FDA are labeled for children, and pediatricians are forced to prescribe medical therapies off-label. The PTN, which is sponsored by NICHD under the BPCA, was created to set up an infrastructure for investigators to conduct trials that improve pediatric labeling and child health. The network studies drugs, primarily off-patent, that lack data in pediatric populations. Its contract was awarded in 2010 and renewed in 2018, with the Duke Clinical Research Institute (DCRI) as the clinical coordinating center and the Emmes Corporation as the data coordinating center. Over 100 sites are involved across the U.S., with several international sites, and they conduct studies in all phases and all therapeutic areas. They have enrolled over 11,000 patients to date and have submitted data on 26 products to the FDA, resulting in 15 label changes.

PTN uses specialized techniques such as advanced PK modeling, blood sampling methods, and leftover samples to efficiently study drugs in children. When designing studies, PTN uses dose-escalating safety trials; master protocols such as the Pediatric Opportunistic PK Study (POPS), which covers several drugs prescribed to children by standard of care, allows the collection of PK samples, and has been used by the FDA to pivot to study COVID-19 therapeutics; and real-world data, which they use to design some studies and extend the findings of others. Dr. Greenberg presented a case study where a neonatologist working in the Neonatal Intensive Care Unit (NICU) had to make an educated guess for the appropriate dosing of the drug acyclovir to treat her young patients with HSV. PTN conducted PK and safety studies for acyclovir in preterm and term neonates and used electronic health record (EHR) data to simulate drug exposures. As a result, they found that clearance of the drug increased over time and the recommended dosing was safe and achieved target plasma exposures in over 90% of infants. The FDA label was updated in 2019 to include dosing by gestational and postnatal age, and clinician dosing guide and Health Canada labels were updated.

To date, PTN has made great strides by focusing on Phase I and II studies and opportunistic studies, drugs for which there are existing indications in older populations, and drugs where efficacy can be extrapolated from older populations. Challenges for the future include large efficacy and Phase III studies which require enrollment of more participants, new indications not currently in the label, and drugs where efficacy cannot be extrapolated. Large pediatric efficacy trials are difficult because they are expensive, they often lack feasibility due to small eligible population or a lack of equipoise, and there is often a lack of understanding of the disease's natural history. Other challenges of large studies include biomarker qualifications, surrogate endpoints and validated endpoints.

For several drugs that lack adult indication, PTN is performing adult studies as requested by the FDA. One of these drugs, methadone, is used off-label in pediatrics to treat severe pain, iatrogenic opioid withdrawal, and neonatal abstinence syndrome. The current drug label shows indications for detoxification treatment and maintenance treatment of opioid addiction, and safety and effectiveness in pediatric patients below the age of 18 years have not been established. There are challenges to adding an indication for the areas for which the drug is currently being used in pediatrics; for pain, it is difficult to extrapolate efficacy, and both iatrogenic withdrawal and neonatal abstinence would be novel indications. PTN is currently conducting a single center study with adult participants to try to understand the PK target at doses used clinically for pain, with the goal of eventually extrapolating these results to children.

Another challenge is making sure that the PTN's important findings become incorporated into clinical practice. PTN enrolled 188 infants in a study to support the use of meropenem for complicated intra-abdominal infections in neonates and infants younger than 91 days, for whom it was not labeled. Dosing recommendations were made as a result of the study, and PTN looked at the EHRs of 2,025 children receiving meropenem to understand how the recommendations were used in clinical practice. The percentage of appropriate doses increased following the release of a paper describing the results of the PTN study, then plateaued for several years. The network hopes to see a further uptick in the future as guidance documents are updated.

Questions and Answers/Day 1 Recap
Perdita Taylor-Zapata, M.D.

Dr. Taylor-Zapata asked the presenters if they had any thoughts on how to expand a non-competitive space where stakeholders from different areas can work together to make progress in PDD. Dr. Tamburro said that NICHD funds several clinical networks such as the Collaborative Pediatric Critical Care Research Network (CPCCRN), which could be leveraged with the PTN to conduct another critical care study. Dr. Greenberg addressed a question in the chat about whether anyone can access the PTN to conduct a research trial. She said that the PTN is an open network and any site can join if they have the relevant population and experience to participate (https://pediatrictrials.org/for-health-care-professionals/). Dr. Mulugeta said that the Critical Path Institute (https://c-path.org/programs/dcc/) would be a good platform to consider for data sharing in a precompetitive environment, and more registries are being developed in a precompetitive space. **Dr. Walson** said that they should be sure to have clinical sites or network sites that are required to produce FDA-compliant data or have experience in regulatory rigorous trials. He added that it would be helpful to have some way of rewarding staff members who are capable of producing viable data. **Dr. Kanecia Zimmerman** said that it is important to have an intentional approach to conducting investigator-initiated trials and network trials.

Dr. Taylor-Zapata reviewed the six gaps identified during the previous day's discussion and introduced the brainstorming sessions.

Cross Collaboration Brainstorming Sessions

Attendees participated in brainstorming sessions focused on specific gaps and proposed solutions. The groups then reconvened and reported out to all participants on the issues, challenges, and solutions that were discussed in the individual brainstorming sessions.

Cross Collaboration Report Out

1). Optimal Trial Development: Developing approaches to "failure analysis" as a means to understand why drugs fail in clinical trials and how such failure might be avoided in the future.

Moderators:
Ravinder Anand, Ph.D.   *Matthew Laughon, M.D.*
Emmes   *University of North Carolina at Chapel Hill*

Rachel G. Greenberg, M.D., M.B., M.H.S.   *Antonello Pileggi, M.D., Ph.D.*
Duke Clinical Research Institute   *OPPTB, NICHD, NIH*

Dr. Anand summarized Group 1's discussion on optimal trial development. In order to address the first identified gap of digital tools to capture PROs, the group considered the example of blood pressure and how it could be captured accurately and consistently to be utilized in regulated clinical trials. They identified many challenges, such as the right cuff size versus arterial line (particularly in neonatal populations) and how the blood pressure is measured, i.e., assessments and adjustments by nurses that are not captured in EHRs. The algorithms used by device companies might not be known and could differ from one company to another, and they could also change without anyone knowing. It can be challenging to engage medical tech companies in the process, and there have been few devices developed for children. In the blood pressure example, metadata must be captured both for research and in clinical practice. Group members suggested that AI algorithms might be utilized for arterial lines, but that would require simulations as a training exercise to better identify the right pressure. More generally, when working with medical tech companies it is best to engage them early in the process and build common interests. Group members from the FDA provided articles to address this issue, which would help to identify what would be acceptable blood pressure in the neonatal population. The group also discussed the fact that while the BPCA program provides incentives to drug companies, there is no similar program for device manufacturers.

The group's second identified gap concerned training in pediatric drug development, specifically gaps in QSP. They discussed how to engage other disciplines in training, developing curricula across different disciplines such as introducing quantitative methods earlier in premed and medical/pharmacy schools. One participant noted that Johns Hopkins University and the University of Michigan have good programs for early collaboration with biomedical engineering programs. Schools of public health, math and statistics programs, and computer science were also mentioned as possible collaborations, specifically early on in the undergraduate stage.

2). Developmental Status of Organ Systems: Understanding developmental status of organ systems metabolism/absorption in young children, particularly neonates.

Moderators:
Alison Harrill, Ph.D.   *Sander Vinks, Pharm.D., Ph.D.*
OPPTB, NICD, NIH   *Cincinnati Children's Hospital Medical Center*

Sara Quinney, Pharm.D., Ph.D.
Indiana University

Dr. Quinney summarized Group 2's discussion on the developmental status of organ systems. For the topic of biomarkers, participants agreed that PK is better understood than PD methods and recommended utilizing the pathway for qualifications guidelines and work with the FDA early on. This could help provide resources to support reproducibility in separate laboratories as well as looking at the specificity of the biomarker. Group members agreed that it was important to encourage biobanking, and all large efficacy trials should have an embedded biomarker aim; well-characterized cohorts with robust outcome data can be better leveraged for future biomarker development as the science changes. One of the group's major takeaways was that biomarkers are currently employed as cutoff measures, but biomarkers change over time, particularly in the pediatric population. It is important to utilize pharmacometrics approaches to evaluate those changes over time. This tied into a discussion on the ways that biomarker data is extrapolated from adults to pediatrics and the need for a clear understanding of the pathophysiology of the system and kinetics of the biomarker, including changes during development which may differ between pediatrics and adults. Verifying assumptions is important, and that could be a role for pharmacometrics and QSP modeling.

The group also discussed drug absorption and the solution put forth on Day 1 of a growing database of PK in adults and children that can be data mined to further understand BCS classification and its application in children. The group felt that the BCS classification system for pediatrics will be more difficult than in adults because of the alterations in absorption, GI tract, drug metabolizing enzyme (DME), and ontogeny across time. The data impacting absorption is often not well reported in the literature, and there is a need to develop an ontology and data dictionary to allow a common data model to use in clinical trials. There are complex issues in pediatrics, especially neonates, and there is not a lot of information on DME, transporter ontogeny, microbiome, gastric pH, and other exogenous factors. Group members suggested that PBPK modeling approaches could help understand sources of variation and better predict absorption based on physiochemical properties of drugs, but they also recognized that these might need to be somewhat drug- or class-dependent approaches. They also discussed the limitation on pharmacometrics training, with limited faculty with the necessary expertise at any one institution and limited internship opportunities in industry. One possible solution to this could be to collect and improve upon online resources, and this is one of the goals of the MPRINT Hub.

3). Integrating Data: Effective utilization of BIG data as well as Electronic Health Record (EHR) or Electronic Medical Record (EMR) integration into clinical research (adult and pediatric).

Moderators:
Lyndsay Avalos, M.D., M.P.H.   *Zhaoxia Ren, M.D., Ph.D.*
Kaiser Permanente Northern Carolina   *OPPTB, NICHD, NIH*

James Feinstein, M.D., M.P.H.
University of Colorado

Dr. Avalos summarized Group 3's discussion on integrating data. To address the gap of insufficient numbers of children to conduct all the needed clinical trials, the group discussed centralizing and harmonizing databases with common data elements and definitions, including PROs. They also talked about data use agreements and challenges with multi-site studies, and agreed that a centralized data use agreement would be helpful. The group also recommended that data sharing from grants and collection of common data elements in grant applications should be encouraged. For data linkages, the group talked about the importance of linking data across children leaving and re-entering health plans so that they can be followed for longer term outcomes. They also discussed linking inpatient and outpatient data, linking a variety of data sources like EHRs, clinical trials, and registries, partnerships with pharmacies and universities to ensure that pharmacy data is entered in the EHR, and the inclusion of methodologists and data scientists on the team. On the topic of decentralized trials, there are unique challenges and opportunities in the pediatric population that must be addressed in order to ensure equity. Finally, the group discussed the early involvement of stakeholders, including patients and caregivers, in order to identify the best ways to collect data and to identify patient-reported outcomes.

Wrap Up, Next Steps, and Closing Remarks
Perdita Taylor-Zapata, M.D.

Dr. Taylor-Zapata summarized the next steps for the BPCA program. The meeting summary and slides will be posted on the meeting website, and the finalized framework resources will be distributed. The BPCA team is in the process of developing a curation plan and team for the framework, as well as a marketing plan for the framework's final home. The BPCA program will follow their usual prioritization process in 2022 and collect input from outside stakeholders, and they hope to expand their outreach and develop a new platform for continued discussions. Dr. Taylor-Zapata said that they anticipate forming three teams centered on training, prioritization, and curation, and they will continue to solicit participation from the meeting attendees. She thanked all of the participants for their time and their contributions to the meeting.

Potential Action Items/Questions to Consider

Potential Action Items
The Foundation for the NIH (FNIH) Biomarkers Consortium is a collaborative effort between the FDA, the NIH, FNIH, and various industry partners. Partnerships like the Consortium can provide a space for multiple companies to work together and support the development, validation, and qualification of a biomarker that can be used by multiple companies. There could be biomarkers and disease indications that garner enough interest to be put forward for consideration in that forum.
It is important to engage other disciplines in training, developing curricula across different disciplines such as introducing quantitative methods earlier in premed and medical/pharmacy schools. Schools of public health (i.e., Johns Hopkins, University of Michigan), bioengineering programs, math and statistics programs, and computer science were also mentioned as possible collaborations, specifically early on in the undergraduate stage.
The PTN is an open network and any site can join if they have the relevant population and experience to participate. The Critical Path Institute would be a good platform to consider for data sharing in a precompetitive environment.

Questions to Consider
Many pediatricians and pediatric clinical researchers are not taught the fundamentals of clinical pharmacology and there is a major need in this area.
Considering an example of blood pressure and how it can be captured accurately and consistently, there are many challenges, such as the right cuff size versus arterial line and how the blood pressure is measured, i.e., assessments and adjustments by nurses that are not captured in EHRs. The algorithms used by device companies might not be known and could differ from one company to another, and they could also change without anyone knowing. It can be challenging to engage medical tech companies in the process, and there have been few devices developed for children. In the blood pressure example, metadata must be captured both for research and in clinical practice.
The use of digital technologies to support decentralized trials offers the opportunity to enroll more patients and more representative patients. This could be especially important for the rare disease population.
There are insufficient numbers of children to conduct all of the clinical trials that need to be completed, and this is especially true for rare diseases and trials where adults are studied first and children are included last with ages slowly being reduced. To address the gap of insufficient numbers of children to conduct all the needed clinical trials, it would be useful to centralize and harmonize databases with common data elements and definitions, including PROs. A centralized data use agreement would be helpful. It would also be useful to link inpatient and outpatient data, linking a variety of data sources like EHRs, clinical trials, and registries, partnerships with pharmacies and universities to ensure that pharmacy data is entered in the EHR, and the inclusion of methodologists and data scientists on the team.

Questions to Consider
It would be good to get a sense of how many fellowship programs exist and potentially partner with organizations like the Pediatric Pharmacy Advocacy Group.
The issue of metabolite profiles is very important, especially in young babies, because a genotype can only predict clearance when there is concordance between the genotype and the phenotype and adult levels of activity for a given enzyme are reached.