Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
2019 Best Pharmaceuticals for Children Act (BPCA)
Stakeholders Meeting
March 22, 2019
6710B Rockledge Drive, Room 1425/1427
Bethesda, MD

The purpose of this meeting, sponsored by the Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), U.S. Department of Health and Human Services (HHS) was to provide updates on the Best Pharmaceuticals for Children Act (BPCA) program. The meeting included invitees representing organizations including, but not limited to the U.S. Food and Drug Administration (FDA), academia, the pharmaceutical industry, and members of pediatric advocacy groups.

Welcome, Overview of Meeting Goals, and Snapshot of BPCA

Perdita Taylor-Zapata, M.D., Program Lead, OPPTB, NICHD, NIH

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 this year's meeting would be more than just reporting back on the overall progress and challenges in pediatric drug development and therapeutics. This meeting also would provide an opportunity for practical discussion not just on what NICHD and BPCA are doing currently, but also what they can do better to further advance pediatric drug development. Dr. Taylor-Zapata also emphasized that presenters would describe some of the challenges they have faced and share lessons learned, but also discuss how they leveraged these challenges into successes. She also offered that this meeting provided a forum to foster collaboration among meeting participants and their stakeholder colleagues.

Dr. Taylor-Zapata next presented a brief overview of the BPCA legislative mandate, explaining that the NIH is to focus on off-patent drugs, and the FDA focus is on-patent drugs. She pointed out that historically, this was an appropriate approach, but that over time, it became apparent that this approach fostered a sense of "silos" and that boundaries are often arbitrary, based more on marketing, rather than on science, resulting in a more exclusionary rather than inclusionary work. Dr. Taylor-Zapata also explained that there has been a recognition that there are common themes across both areas. The current thinking is to build bridges to foster and facilitate collaboration. Some of these cross-cutting "bridge" issues include:

- Developing clinically meaningful outcome measures
- Validating biomarkers
- Extrapolating from adult to pediatric studies
- Addressing workforce issues (e.g., ensuring that sites have been trained to conduct these types of trials)

Dr. Taylor-Zapata next summarized the key concerns that the BPCA was meant to address when it was first initiated in 2004:

- The large number of drugs that lack data on appropriate dosing, efficacy, and safety for neonates, infants, children, and adolescents
- Data gaps as evidenced by the lack of pediatric labeling
- The lack of knowledge on the conditions that bring children to the health care system and how they are treated
- The limited number of drugs formulated for pediatric, rather than adult, usage
- Inadequate data on dosing, efficacy, and safety resulting in deficits in drug labeling and harm to children.

Dr. Taylor-Zapata pointed out that while the BPCA program is still struggling with establishing and solidifying its identity, during the past 15 years, an impressive amount of progress has been made:

- More than 700 drug label changes have been made through BPCA and the Pediatric Research Equity Act (PREA).
- To date, 25 Clinical Studies have been submitted for label change. (Clinical drug development studies are being done without having clinical drug developers at the table).
- A total of 9 label changes have been made through the NIH BPCA program.

She explained that the process of selecting drugs for potential label change begins with determining priorities, based on:

- Emerging safety concerns
- Public input
- Research gaps identified by FDA and academia.

The selected priority areas are included in a priority list. From that list, the determination is made on clinical studies that can be done. To date, BPCA has prioritized 150 drugs, with 50 specific therapeutic categories/areas. Dr. Taylor-Zapata pointed out that of those 50 therapeutic areas, approximately half are areas being currently studied.

She briefly described the current 22 BPCA therapeutic areas covering neonates to teens, from the intensive care unit (ICU) to outpatient settings, covering multiple therapeutic areas. More than 120 drug moieties are being studied to date. As noted earlier, nine label changes (including one device) have been made through NIH BPCA since 2012, with the most recent change in 2019. These changes address a broad spectrum of diseases/conditions affecting a broad pediatric population in different settings, including the ICU. Dr. Taylor-Zapata noted that this broad reach allows BPCA to have a perspective that cuts across therapeutic areas and multiple themes. On the other hand, it requires dealing with more than one organizational focus area, for example, more than one FDA division.

Dr. Taylor-Zapata presented an overview of FDA submissions from 2015-2016 and from 2017-2018. These submissions are still pending FDA review and approval for label changes. She also indicated those that are posted on the Data and Specimen Hub (DASH).

Dr. Taylor-Zapata concluded by emphasizing that the goal of this meeting was to engage in valuable and constructive dialogue on how to move forward in advancing the BPCA mandate.

Pediatric Trials Network: Achievements and Future Directions

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

Dr. Benjamin began by acknowledging the junior and mid-career faculty as the journeymen who are the crux of the Pediatric Trials Network (PTN). He also recognized that the structure of the PTN has evolved since it was first established in 2010. Senior faculty are also involved; their experience, including their experience in failed trials, has proven invaluable.

Dr. Benjamin reiterated the PTN mission: "Create an infrastructure for investigators to conduct trials that improve pediatric labeling and child health." He also explained that the PTN focus, like that of BCPA, is on off-patent therapeutics. Dr. Benjamin reviewed the PTN organizational structure, elaborating on Dr. Taylor-Zapata's earlier presentation. He emphasized that this distributed leadership model, with only two committees, has been successful in "pushing out" work and study funding.

He explained that based on the NIH priority list of off-patent therapeutics, investigators submit a study concept sheet to PTN, which the PTN Administrative Core reviews for science and feasibility. The PTN Steering Committee then also reviews the study concept science and feasibility. If approved, the PTN forms a protocol development team, comprised of a protocol chair, thought leaders, pharmacologists, and operations experts. The PTN then selects sites based on site study interest, availability, and previous history of enrollment. The PTN moves ahead and executes the trial.

Dr. Benjamin next presented a list of the various U.S. and international partnerships and collaborations currently part of the PTN. He then compared the original contracted PTN scope of work (SOW) with what has been accomplished to date. The initial SOW anticipated 16 clinical trials; to date, a total of 38 studies have been accomplished. The original SOW involved 6 therapeutic areas; 18 have been addressed so far. The initial SOW required enrolling 1,600 children compared with almost 8,000 currently enrolled. There have been 21 product submissions compared with the 4 anticipated in the original SOW. Dr. Benjamin also pointed out that the PTN now has both a domestic and global enrollment reach.

Dr. Zimmerman reviewed a number of challenges in clinical trials that investigators typically face:

- Limited number of patients
- Limited blood volume
- Perceived study risks – blood draws
- Variability in site enrollment and contracting
- Competing research priorities
- Low consent rates
- Lack of validated endpoints
- Limited research funding
- Lack of trained pediatric clinical investigators
- Lack of pediatric clinical pharmacology expertise.

She then briefly discussed some of the approaches that the PTN has taken to address these challenges.

Challenge: Limited Number of Eligible Patients
Solution: Microtrial inclusion/exclusion criteria and sample size negotiation

These studies usually require large sample sizes. At the same time, they require very limiting inclusion and exclusion criteria. Dr. Zimmerman cited the meropenem trial as an example of successfully negotiating trial design and sample size with FDA, resulting in an FDA label change.

Challenge: Limited Blood Volume
Solution: Sensitive drug assays and minimal sampling methods

Dr. Zimmerman briefly listed several mechanisms, including collecting low-volume plasma samples, as well as dried blood spots and multiplex assays as ways to minimize collecting of blood from pediatric study patients.

She also noted that the PTN advocates implementing population pharmacokinetics. She described the Duke Clinical Research Institute (DCRI) Pharmacometrics Center as a resource for providing clinical pharmacology support for all stages of clinical trials. The Center works across industry and Government to provide pharmacokinetic/pharmacodynamic (PK/PD) analyses, modeling, and simulation expertise and guidance for special populations, including pediatric populations.

Challenge: Site Variability and Prolonged Time to Establish Site Contracts
Solution: PTN –Sites and Rapid Start Network

Dr. Zimmerman described the DCRI Rapid Start Network, an academic and community-based network of currently more than 200 members from the US, UK, Canada, Israel, and Singapore. The network addresses diverse therapeutic areas, from preterm to adolescent populations. The aim of the Network is to maintain relationships with members through site input into protocol design and feasibility, site materials, and identification of barriers to enrollment.

Solution: Master Protocols - PK of Understudied Drugs: Administered to Children per Standard of Care (POPS)

Dr. Zimmerman also described using master protocols to examine the PK of understudied drugs administered to children. She cited the example of the Pediatric Opportunistic PK Study (POPS) master protocol. Dr. Zimmerman noted that the POPS study involves more than 50 drugs with 3,000 patients enrolled to date, with approximately 40 new enrollees each month, including special populations.

Challenge: Competing Research Priorities
Solution: Protocols Complement and Fill Gaps

Dr. Zimmerman described the NICHD Neonatal Research Network. She noted that with a primary focus on randomized controlled trials in premature infants, co-enrollment is problematic for this initiative. She explained that co-enrollment is discussed with potential site investigators during the PTN site selection process. She also pointed out that the PTN allows for co-enrollment in more than one PTN study, if limitations on safe blood volume drawn are followed.

Challenge: Low consent rates
Solution: Improve Parent/Participant Engagement
Solution: Design Trials Relevant to Current Public Health Issues - PK and Safety of Commonly Used Drugs in Lactating Women and Breastfed Infants (CUDDLE)

Dr. Zimmerman acknowledged that low consent rates are not surprising, that they are based on clinician concerns about parental burden, as well parental concerns about study invasiveness and lack of clarity of benefit to the child. She described several initiatives to reach out to and better engage parents. She noted that one approach has been to send thank you notes to parents for participating in a study conducted by the PTN. She also described launching studies that are relevant to the general public, for example, the newly opened protocol studying drug concentrations in breast milk and plasma.

Challenge: Lack of Validated Endpoints to Solution (or Response): Endpoint Validation per FDA Guidance through Use of Existing Infrastructure

Dr. Zimmerman noted that the lack of validated endpoints, especially endpoints that are clinically relevant, is problematic. These endpoints must be responsive to treatment and disease progression; they must be reproducible, and they must be reliable and developmentally appropriate. She cited the Anesthetics and Analgesic Master Protocol as an example of using existing infrastructure through FDA guidance to collaborate with the original study developers and recruit subject matter experts to establish validated scales for future use in drug development.

Challenge: Limited Funding
Solution (or Response): Identify additional funding sources

Dr. Zimmerman outlined several potential sources of study funding. These resources include NIH/FDA ancillary funding through leveraging the PTN infrastructure; assisting with current studies; and pursuing K23, R01, and K24 grant program opportunities. She also encouraged

participants to partner with industry, noting that industry funds can be used to cover drug costs, reduce site expenses, and reduce overall study costs.

Challenge: Lack of Trained Investigators
Solution: Partner with Sites; Develop a Pipeline

Dr. Zimmerman reminded participants that an important part of the PTN is that it provides a source of hands-on, real-time experience. She cited the partnership with the NIH Institutional Development Award (IDeA) States Pediatric Clinical Trial Network (ISPCTN). The ISPCTN provides experience in contract negotiation, site activation, and collection of clinical data. She also described the R25 program, which provides an opportunity for high school and college students, and some educators to gain hands-on clinical research experience resulting in publication.

Challenge: Lack of Pediatric Clinical Pharmacology Expertise
Solution: Collaborate with PTN to Increase Partnerships

Dr. Zimmerman described the UNC-Duke Collaborative Clinical Pharmacology T32 Postdoctoral Training program as an example of successful collaboration with NICHD, the National Institute of General Medical Sciences (NIGMS), and academia to expand the pipeline of pediatric clinical pharmacology expertise. She also discussed the program's collaborative initiatives with PTN, focusing on data sharing, thought leadership, and clinical trial operations, resulting in 25 peer-reviewed publications.

Dr. Benjamin briefly summarized key lessons learned during the past 9 years. He emphasized the need to incorporate these lessons into future activities, given the possibility of no increase of funding levels in the foreseeable future:

- Collaborate and have frequent discussions with key partners (e.g., NICHD, the BPCA Data Coordinating Center (DCC), FDA, and sites and investigators)
- Maximize protocol efficiency (through simple design, system and organization controls, standard of care (SOC) procedures, inclusion criteria, multiple drugs, and efficient data analysis methods)
- Maximize operational efficiency (through master contracts, careful site selection, site metrics, and template documents when appropriate).

He then pointed out some key elements in charting the future direction of the PTN:

- Further partnership with industry
- Regulatory certainty (approved trial design for off-patent drugs will serve as a model for new therapeutics)
- Broad therapeutic expertise (including infectious diseases, critical care, rheumatology, cardiology, neonatology, pharmacology, neurology, and pulmonology)
- Enrollment of control arm for new therapeutics
- Passive data extraction in clinical trials, for example, electronic health records (EHRs), as a resource)

- Registries for long-term follow-up and cohort identification.

Dr. Benjamin urged participants to consider building on the success of K23, K24, and K9 programs, as well as those grant programs mentioned above, and to replicate those successes nationwide. He emphasized the importance of engaging parents and families, as well as researchers, not only in a circle of learning, but in a circle of community engagement. He referred to the R25 program as an example of a non-traditional approach. To date, more than 100 high school and college students, and some educators partner directly with fellow and junior faculty. This hands-on exposure to clinical research methods has led to publication in peer-reviewed journals.

Dr. Benjamin concluded by pointing to other examples of sources of collaboration, information-sharing, and funding. He noted that the DCRI is the coordinating center looking at the need for further capacity building for the IDeA States. He also mentioned that the PTN will continue partnering with the Eco Program, which is examining opioid trials. He referred participants to other potential partners and/or networks, such as the Innovation Network, as avenues for reaching out to parents and families, and even involving children in study trial design and protocols.

Question (Dr. Kelly): Through the BPCA/NICHD, is there funding to actually conduct the trial, or is it just infrastructure? In other words, if there is a study idea, do you have to submit an R01 to get funded to do that? Can you talk more specifically about how that works?
Response: Dr. Benjamin reiterated that the congressional mandate requires that PTN funds are to be allocated to focus on labeling. He reviewed the process that he described earlier in his presentation, noting that the PTN works with researchers, and engages in dialogue with them to help "frame" the study purpose with a labeling focus.
Comment: Dr. Hazra pointed out that biomarkers are included under the current PTN mandate, but those biomarkers must be directly relevant to labeling to be approved for funding through the PTN.

Progress and Challenges in Pediatric Drug Development

John Alexander, M.D., M.P.H. Deputy Director, Division of Pediatrics and Maternal Health Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA)

Dr. Alexander began by emphasizing the guiding principles that were, and continue to be, the basis for this program:

- Pediatric patients should have access to products that have been appropriately evaluated.
- Product development programs should include pediatric studies when pediatric use is anticipated.

In presenting an overview of key milestones and legislation related to pediatric drug development from 1902–2017, Dr. Alexander pointed out that drug development has been based on what is useful and helpful for most of the "population"—that is, adults. He emphasized that the goal of this program is not to study every drug, only the drugs that have a potential public

health implication for the pediatric population. He also noted that much of the early legislation came about as the result of responding to specific incidents or actions that were harmful to children or that addressed FDA operational requirements. Dr. Alexander also emphasized that while many of these separate pieces of legislation have resulted in positive changes, until fairly recently, the over-riding approach to pediatric drug development has continued to be based on the guidance that the best way to protect children was not to do research on children.

Dr. Alexander then focused on the current state of pediatric drug development, noting that as of January 30, 2019, a total of 772 products are now labeled with pediatric-specific information. Of those, 186 labels are due to BPCA legislation; 420 labels are due to PREA requirements; 49 are results of the Pediatric Rule (pre -PREA), and 117 are due to both.

Dr. Alexander discussed the rate of pediatric labeling changes between 1998 and 2018, noting that few changes occurred initially, but that in 2018, between 40 and 50 labeling changes occurred. He singled out two recent changes, noting that off-patent drug labeling was approved for lithium in October 2018 (for pediatric patients aged 7 years or older with bipolar I disorder). Off-patent labeling was also approved for acyclovir in January 2019 (for neonatal herpes simplex virus infections).

Dr. Alexander next summarized the continuing challenges that are inherent to pediatric research:

- Pediatric population size
- Studies divided by age groups
- Clinical research in pediatric patients
- Time lag for completion of pediatric trials
- Pediatric networks
- Neonatal diseases.

He pointed out that clinical research in pediatric patients is always difficult due to the need to have special safeguards in place to protect pediatric subjects. Pediatric-focused research studies cannot rely solely on previous adult studies. He emphasized the impact of the considerable time required to complete pediatric trials. He pointed out that many U.S. and international pediatric networks are still in development; we will continue to put together networks to study different diseases in different clinical care environments.

Dr. Alexander noted that since PREA enactment, the FDA has gained increased experience in putting in place appropriate study trial designs, and in translating efficacy from adult studies into pediatrics. He cautioned that the FDA will face additional challenges as it moves forward into expanded or broader studies, including:

- Pediatric-specific conditions
    - Rare pediatric disease designation
    - Pediatric oncology (molecular targets)
- Real world data versus real world evidence
    - Still being evaluated in demonstration projects (mostly in adults)

- Drug pricing
- Changing pediatric practice.

Dr. Alexander pointed out that researchers also must determine how to design studies of diseases/conditions specific to pediatrics that are not studied in adults. He cautioned that real-world data and real-world evidence are not the same thing, and that use of real-world evidence is still being evaluated, mostly in adult studies. While the FDA is not involved in drug pricing, Dr. Alexander noted that the current congressional environment (and overall concerns regarding health care costs) could be problematic for allocating funds for future drug development research. He also noted that it will be increasingly important to consider changing pediatric practice. From these studies, we are getting more information on how certain drugs could be used, but we are still not clear about how to translate that information into clinical practice.

Dr. Alexander concluded his presentation by offering several key points:

- Celebrate the progress made in accumulating pediatric clinical trial information (labeling).
- Emphasize that children are protected through research.
- Recognize and address continuing challenges inherent to supporting pediatric clinical research.
- Understand the additional challenges to be faced in moving forward in other pediatric areas of need.

He reiterated that the FDA is committed to working with external stakeholders to improve efficiency of pediatric clinical trials and in developing innovative clinical trial designs (including use of bid data), and improved framework for pediatric extrapolation. Finally, the FDA is committed to supporting clinical trial networks and international collaborations.

Implementing FDARA 2017 Provisions: Facilitating Precision Cancer Medicine for Children

Gregory H. Reaman, M.D., Associate Director, Oncology Sciences, Office of Hematology and Oncology Products, Office of New Drugs (OND), CDER, FDA

Dr. Reaman began by presenting an overview of cancer drug development for children and teens. He pointed out that the biologic, societal, and economic challenges to developing drugs for children and teens have been recognized as far as back 55 years, with the study of children with acute leukemia, even before the founding of the National Cancer Institute (NCI). He emphasized that in addition to the challenges inherent in developing drugs for children and teens, developing drugs for the pediatric cancer population presents specific and somewhat unique challenges that warrant discussion. While pediatric drug development widely leverages adult drug discovery/development, there are very limited opportunities for extrapolation and limited pre-clinical testing in pediatric cancer models. In addition, the impact of legislative initiatives that support pediatric drug development has been markedly less obvious in oncology than in other clinical areas. In addition, many targeted agents that are likely applicable to cancers in children are delayed further due to application of the new drug development paradigm.

Dr. Reaman explained that this paradigm shift has been evolving during the past 10 to 15 years. Dating back to the 2003 human genome project, this paradigm is based on genomic and proteomic interrogation of individual cancers screened for specific molecular abnormalities for which "highly specific" targeted agents are developed. This has resulted in creation of multiple rare subsets (defined by molecular phenotype) of previously common cancers, which has resulted in the widely accepted concept that tumors are defined by molecular origin rather than histology. Most of the new cancer drug approvals are for targeted agents for biomarker-defined populations and subsets.

Dr. Reaman cited the example of the evolution of identification of genomic alterations in lung cancer, noting that as recently as 20 years ago, clinicians and researchers knew there were small-cell cancers and non-small-cell cancers. Today, the molecular drivers of these tumors are commonly known and identified. He compared the challenges of the "old paradigm" with the challenges presented by the "new paradigm." Dr. Reaman noted that the old paradigm has largely disappeared. In the old paradigm, there was a high risk for Phase 3 failure or clinically small effect. With the new paradigm's target therapy approach, there is greater likelihood for achieving a large, clinically meaningful effect. He pointed out that more than 50 percent of pediatric cancers have druggable molecular abnormalities.

Dr. Reaman next summarized key U.S. drug development legislation, specifically, comparing PREA and BPCA:

- PREA covers drugs and biologics
  - Mandatory studies, only on indication(s) under review
  - Orphan indications are exempt from studies
  - Pediatric studies must be labeled.
- BPCA covers drugs and biologics
  - Voluntary studies with incentives
  - Studies relate to entire moiety and may expand indications
  - Studies may be requested for orphan indications
  - Pediatric studies must be labeled.

Dr. Reaman next summarized key elements of the Research to Accelerate Cures and Equity (RACE) for Children Act. Incorporated as Title V of the FDA Reauthorization Act (FDARA), enacted August 18, 2017, the RACE for Children Act requires evaluation of new molecularly targeted drugs and biologics "intended for the treatment of adult cancers and directed at a molecular target substantially relevant to the growth or progression of a pediatric cancer." It also defines molecularly targeted pediatric cancer investigation. Arguably the most important change to the Act has been the elimination of the orphan exemption for pediatric studies for cancer drugs directed at relevant molecular targets.

Dr. Reaman also reviewed the definition of "molecular target" and summarized the statutory requirements related to targets for FDA, to be implemented by August 2020. These requirements include establishing and maintaining on the FDA website a list of "relevant" targets, as well as establishing and posting a list of targets (non-relevant) leading to waivers of pediatric studies.

Other statutory requirements include working with NCI, the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC), the Trans-NIH Pediatric Research Consortium (N-PeRC), investigators, sponsors, experts, and advocates on implementation and required studies, as well as convening an open public meeting to generate/finalize lists and issuing guidance on implementation.

Dr. Reaman described current FDA implementation efforts, including mechanisms to engage internal and external stakeholders, such as open public meetings, as well as planning and implementation efforts coordinated with internal FDA programs (e.g., OHOP/OCE, OPT, OCP, DPMH, ORP, and OCC). He pointed out the increased focus on accelerating appropriate initial pediatric evaluations, rather than increasing number the of pediatric phase 1 studies. The FDA also is engaged in advising sponsors of new conditions and requirements for initial pediatric study plans (iPSPs) for new applications with planned submission dates after August 18, 2020.

Dr. Reaman next reviewed the framework for defining relevance developed during the multi-stakeholder workshop sponsored by Friends of Cancer Research:

- Presence of target in one or more pediatric cancers- not prevalence-dependent
- Target function- etiology, drug resistance, lethality
- Non-clinical evidence- general and pediatric-specific
- Adult clinical experience
- Predictive/response biomarkers availability
- Accessibility for immunotherapy-directed targets
- Therapeutic agent available/in development.

Again, Dr. Reaman emphasized that the focus is on accelerating the process by facilitating appropriate initial pediatric evaluations early in the development timeline, and not increasing the number of pediatric phase 1 studies.

Target Lists. He then discussed target lists, noting that these lists have been developed in response to the statutory requirement to address regulatory uncertainty for industry and guide (not dictate) decision-making regarding early evaluation of a specific agent as an amended PREA requirement through the iPSP process. He also explained that being designated as relevant is neither an absolute nor an exclusive requirement for decisions related to pediatric evaluation—studies of new products may be required for a drug whether or not that drug is on/not on a target list. The designation process is not envisioned to restrict authority or flexibility, and relevant molecular targets are independent of agent and/or biomarker availability. Candidate target lists were constructed by the FDA's Oncology Center of Excellence (OCE) with NCI and with input from international content experts; they were reviewed in open public meetings, with no pre-specified minimum evidence base.

Dr. Reaman briefly reviewed the following types of target designations:

- Targets Associated with Specific Gene Abnormalities
- Targets Associated with Cell Lineage Determinants

- Targets on Immune Cells and Cellular Components of the Tumor Microenvironment
- Targets that focus on pathways and functional mechanisms.

Dr. Reaman explained that non-relevant targets receive "automatic" waivers. He briefly described certain factors that warrant consideration for a waiver. These factors include serious developmental toxicity; second or third "in class" product without compelling evidence of substantial differences in efficacy, safety, PK profiles, or formulation to warrant additional pediatric studies; and feasibility and practicability due to small study populations

Dr. Reaman reiterated the requirement that FDA publish and maintain these lists and that the Agency conduct semi-annual workshops to solicit input and remarks from the public. The current target lists are posted on the OCE Pediatric Oncology Program website and encouraged participants for their comments on existing targets and suggestions for additions/deletions.

Dr. Reaman presented a list of factors to be considered in the decision-making and prioritization process:

- Likely variable by target class and disease
- Prevalence of target expression in a single disease or across histologies, evidence that target inhibition modulates tumor growth
- Extent of unmet clinical need or potential public health impact
- Availability of and access to agent
- Availability of predictive or response biomarkers
- Collaboration between Industry and clinical investigator community: Multi-stakeholder input required to inform FDA decision-making
- Clinical and/or pre-clinical evidence of activity
- Toxicity profile
- Potential benefit: risk assessment
- Formulation
- Multiple agents in class: transparent evaluation of selection criteria in pre-competitive space
- Rare pediatric cancers not well supported by current study platforms; innovative designs/solutions.

While pediatric drug development presents significant challenges, Dr. Reaman noted that the FDA will continue to identify creative ways to meet these challenges, including:

- Uniform international master protocols for biomarker-directed studies- efficient and high-quality data
- Increased extramural input while respecting proprietary considerations
- Early pipeline presentations; possible industry collaboration
- Industry-initiated public-private partnerships, especially for pediatric pre-clinical models.

He emphasized that successful implementation will require transparency among all stakeholders to:

- Address anticipated, potentially adverse consequences
- Initiate early pediatric pre-clinical testing initiatives through effective industry-academic collaboration (public-private partnerships)
- Recognize emerging scientific discovery.

Dr. Reaman concluded by underscoring the importance of global coordination, emphasizing that global development requires international collaboration in designation of relevance, prioritization, and decision-making regarding study feasibility and conduct. He reiterated the importance of supporting/encouraging international trials to avoid costly and unproductive duplication and competition. He noted that global coordination efforts should continue to build on current activities, including priority setting of relevant targets through periodic international, multi-stakeholder workshops and through continuing Pediatric Cluster Call discussions of pediatric investigation plans (PIPs)/iPSPs. He also noted that plans are underway for changes to PREA international expansion of the EU ACCELERATE Platform.

Question (Gipson): We're looking with great expectation for the impact of this legislation. We in pediatric nephrology – and so many others – have the same challenges. Children with Orphan diseases do not have the opportunity to participate in drug development and testing in children is not required, consequently, treatment of children with orphan diseases continues to lack safety, efficacy and dosing information necessary for safe practice. Do you have suggestions on how to replicate or expand the RACE legislation for non-oncology therapeutic areas?
Response: Dr. Reaman noted that legislative changes and amendments to PREA resulted from parent advocacy and organized lobbying efforts from groups supporting children with cancer. From the very beginning of PREA and BPCA, it was recognized that the work of these programs would never have direct benefits for children with cancer. The orphan designation has clearly helped in encouraging development of drugs for rare diseases. However, the exemption that precludes children with these rare diseases from these studies needs to be thoroughly investigated, and legislative repercussions assessed.

Question (Ward): What is the number of identified targets that have pediatric relevance?
Response: Dr. Reaman acknowledged that many of the targets of interest are unique to pediatric malignancies. He pointed out that it is still a challenge to convince industry to develop drugs that are specific for those relevant targets.

Facilitating Pediatric Drug Development in Gastroenterology: Current Challenges and Opportunities

Tara Altepeter, M.D., Medical Officer, Division of Gastroenterology and Inborn Errors Products, OND, CDER, FDA

Dr. Altepeter began by reiterating that pediatric patients are traditionally studied after adult studies are completed and a new drug is approved for adults. This methodology results in delays between an adult approval and a pediatric approval that typically average 8 to 10 years. She further noted that during that time, there is often widespread off-label use of drugs, which puts

pediatric patients at risk due to uncertainties regarding safety, efficacy, and appropriate dosing. In addition, this significant lag time results in lost opportunities to collect data in a controlled and monitored clinical trial setting. Dr. Altepeter also noted that recent efforts to decrease delays in initiation and completion of pediatric studies have not yet resulted in much improvement, thus continuing to place a burden on pediatric patients and their families seeking access to newer therapies.

She explained that she would focus her presentation on discussing the challenges and opportunities for improvement in facilitating drug development across two different gastroenterological (GI) conditions—functional GI disorders and inflammatory bowel disease (IBD). She explained that functional GI disorders (or newly referred to as "disorders of the brain-gut axis") have always been particularly challenging to study, even in adults. This umbrella term covers irritable bowel syndrome (IBS), as well as idiopathic constipation that is, pediatric functional constipation (PFC) in children, and functional diarrhea.

Dr. Altepeter briefly described pediatric IBS epidemiology, pointing out that while IBS, including PFC, affects an estimated 3-20 percent of children, it is more common in older children and adolescents. Constipation-predominant type (IBS-C) is much more common than diarrhea-predominant or mixed type. However, the subtype may change over time, presenting an additional challenge when studying these conditions. She also emphasized that IBS pathophysiology is complex, involving a considerable number and range of factors that are not completely understood, thus making drug development even more challenging.

Dr. Altepeter next discussed the current labeling status for pediatric IBS therapies. She pointed out that five therapies have been approved and are available for adults. However, none of the five has been successfully studies and labeled for pediatric IBS patients.

Dr. Altepeter next discussed current challenges and potential opportunities to mitigate those challenges:

- **Challenge:** There is a substantial psychosocial component that influences severity of symptoms and potential response to treatment.
  Opportunity: Efforts to standardize behavioral modification (acknowledged to be an important part of holistic approach to functional GI conditions) for all participants might help account for this concern within a trial.
- **Challenge:** Treatment effects for available therapies approved for adults are modest, and historically placebo response rates are high.
  Opportunity: Implementation of a run-in period with re-screening to ensure symptoms persist between initial screen and randomization may reduce rate of placebo response.
- **Challenge:** Endpoints are measured by patient-reported outcome (PRO) tools.
  Opportunity: A composite endpoint for IBS is "responder"- based, using PRO data on both abdominal pain and stool-related signs (frequency in IBS-C and consistency in IBS-D). Ongoing work is needed to better understand the most impactful aspects of the disease in children, and determine if they change with treatment, to inform future trials.

Dr. Altepeter next discussed IBD, noting that IBD includes Crohn's disease (CD) and ulcerative colitis (UC). IBD affects an estimated 1.3 million patients in the United States, most of whom are adults. She explained that the two conditions are related, but distinct entities. Both conditions are chronic, lifelong autoimmune disorders affecting the GI tract, characterized by significant morbidity, reduced quality of life, and at times, increased mortality. Both conditions require long-term treatment for optimal management. Like IBS, IBD pathophysiology is not completely understood, but it includes the interplay between genetic susceptibility and environmental factors/triggers.

Dr. Altepeter pointed out that 25 percent of IBD cases are diagnosed in childhood, with peak onset during adolescence. Approximately 5-10 percent of all IBD patients in the United States are less than 18 years of age, making IBD relatively rare in childhood. The goal of treatment is to achieve a stable, durable state of disease remission, including minimizing bothersome symptoms, healing the inflamed mucosa, and avoiding surgery and other complications (e.g., colon cancer).

In discussing the current labeling status for pediatric IBD therapies, Dr. Altepeter pointed out that of 10 possible therapies for adults, only 3 are labeled for children. Also, five drugs have been approved for treating moderate to severe UC and CD, but only one of those five has been approved for pediatric UC, and two of the five have been approved for treatment of pediatric CD.

Dr. Altepeter next discussed some of the barriers to timely completion of pediatric studies. She noted that several medications approved for adult IBD have become the standard of care in pediatric IBD clinical practice, leading to difficulties with study enrollment. It is understandable that patients and families may be less willing to take on the additional burden of trial participation, when the drug is accessible to them off-label through their healthcare provider. Dr. Altepeter also noted that clinicians may be less inclined to participate in, or refer patients to participate in, a trial for a therapy that is widely regarded as effective based on accumulating anecdotal experience. Study designers are also having to consider the ethics of including vulnerable subjects in research.

Dr. Altepeter pointed out that early enrollment of adolescents has been considered as a potential solution to several of these challenges. She also listed factors that should be weighed when considering this approach:

- Sufficient similarity in disease progression and anticipated response to therapy between adult and pediatric patients to support extrapolation
- Prospect of direct benefit to pediatric patients
- Adequate preliminary dosing and PK information to support dose selection in adolescents
- Adequate nonclinical and preliminary clinical safety data in adults to support use in pediatric patients.

Sufficient Similarity. Dr. Altepeter explained that sufficient similarity in disease progression and response to treatment between adult and pediatric patients is generally accepted by the IBD community and FDA. Although many treatments are used off label, treatments that are useful in adults have been shown to have similar treatment effect in pediatric patients, although few controlled clinical trials have been conducted in this population. Reports on the safe and

effective use of many of these medications have not identified any examples where a treatment that is efficacious in adults does not benefit pediatric patients.

Prospect of Direct Benefit. Dr. Altepeter reminded participants that according to Federal statute, **"**an investigational drug which incurs more than minimal risk… must offer the prospect of direct benefit to individual subjects." She noted that initially, the prospect of benefit was interpreted by both the FDA and industry sponsors to mean clearly confirmed efficacy data in adults. However, the standard is changing to meet the evolving needs of pediatric patients and families.

Adequate Preliminary Dosing and PK Information to Support Dose Selection. Dr. Altepeter cautioned that dose selection is crucial. Robust data from phase 2 adult studies that support that chosen dose(s) are likely to be efficacious is an absolute requirement for this approach. Data across a wide variety of drugs and diseases support the assertion that adolescents can generally be treated with the same dose as adults and expect similar systemic exposure. There must be sufficient similarity in disease progression and anticipated response to therapy between adult and pediatric patients to support extrapolation. There also must be the prospect of direct benefit to pediatric subjects. In addition, there must be adequate preliminary dosing and PK information to support dose selection.

Adequate Nonclinical and Preliminary Clinical Safety Data. Dr. Altepeter pointed out that there must be enough clinical data to support the premise that early use in pediatrics would be reasonable. While the extrapolation concept applies to efficacy, and not safety, Dr. Altepeter cautioned that enrolling adolescents before a final characterization of the risk/benefit profile of a drug (i.e., pre-approval setting) requires careful consideration of the known and anticipated risks to pediatric patients. It is also important to acknowledge that waiting to achieve "certainty" is not always in a pediatric patient's best interest.

Dr. Altepeter also discussed operational factors to be considered, including:

- Site selection, with the option of referring adolescents to an adult site for trial participation, or opening new sites at higher volume pediatric centers to run the same program.
- Trial design, including placebo control; number of blood draws, visits, and assessments; and performance characteristics of certain PRO tools developed for use in adults that may not be well established, particularly in younger adolescents.

She also pointed to other factors such as timing of implementation and sample size of sub-population that should be considered. She cautioned that some safety issues may not be fully apparent at the outset. Therefore, it is critical to enroll a truly representative study sub-population.

In closing, Dr. Altepeter emphasized that including adolescents in adult phase 3 trials is new to the IBD study environment, and, therefore, is currently not met with enthusiasm by all stakeholders due to:

- Concerns about differences between FDA and other regulatory bodies, including international organizations
- Reluctance to expose pediatric patients to an "unknown"
- Uncertainties regarding whether a small number of enrolled pediatric patients will be adequate to support an early approval below age 18
- Perceived risk to adult program (efficacy or safety related) on the part of industry sponsors.

She emphasized that this approach has been demonstrated to be successful in some disease areas. Based on those successes, she argued that this approach warrants consideration for IBD studies. Despite industry's somewhat misguided concerns regarding inclusion of adolescents in adult studies, this approach remains one of several potential strategies aimed at achieving a shared goal of collecting adequate data in pediatric patients to appropriately label drugs for safe and effective use in a timely manner.

Addressing Challenges in Pediatric Drug Development: Pediatric Nephrology

Debbie S. Gipson, M.S., M.D., Professor of Pediatrics, Division of Nephrology, University of Michigan

Dr. Gipson opened her presentation by citing data that attest to the need to address chronic kidney disease as a major public health issue concern, noting that currently, 9,721 children are living with end-stage kidney disease (ESKD), also noting that ESKD can reduce life expectancy by 10-50 years.

Dr. Gipson next identified numerous, interlocking factors that have been identified as barriers to pediatric drug development, explaining that these barriers have been identified by patients, their families, and other stakeholders. She explained that she would focus her presentation on "cultural" issues and barriers. Dr. Gipson emphasized that the almost-universal agreement for the need to protect children ***from*** research has evolved to a view that we must protect children ***through*** research.

Dr. Gipson described the community approach to addressing these barriers, noting that these solutions are complicated; they require a workforce, community involvement, and buy-in. She explained that she would discuss three examples of projects that have incorporated patient-provided information into their community approach. She emphasized that while researchers have made significant progress in collecting and organizing information from a range of data sources, investigators are less adept at identifying and including critical, and arguably as important, information from the patient and/or caregiver.

The first example cited by Dr. Gipson was an international study that focused on prioritizing, developing, and validating clinical outcome measures based on purpose, age, and disease. The Standardised Outcomes in Nephrology for Children and Adolescents (SONG-Kids) study was

aimed at identifying a core set of outcome measures. In reviewing 205 trials, 100 domains of outcome measures were used, making it very difficult to compare data across so many clinical trials. Led by a team in Australia, a multi-stakeholder group, including pediatric and adolescent patients, as well as caregivers, replicated an adult model for pediatrics. The SONG-Kids study team also included clinicians, clinical scientists, regulators, and facilitators from several countries. The study allowed for both in-person and Web-based participation. Dr. Gipson then reviewed the top 10 outcomes ranked by group—patients, caregivers, and health professionals. Quality of daily life was much more important for patients and caregivers than for health professionals. The first three top-ranked outcomes—life participation, mortality, and kidney function—were the same for patients and caregivers. However, health professionals indicated different priorities than patients and caregivers, ranking life participation fifth.

Dr. Gipson next discussed the second example, the Kidney Health Initiative (KHI). A public-private partnership among the American Society of Nephrology, the FDA, and more than 90 companies and organizations related to kidney disease, the KHI has been created to provide an environment where these multi-stakeholder groups can collaborate to promote development of new therapies and improve the quality of life for individuals living with kidney disease.

Dr. Gipson discussed a CDER-funded KHI project aimed at overcoming barriers to drug development in children with chronic kidney disease (CKD). The study is focused on:

- Recognizing the legal and regulatory framework for pediatric study plans in the U.S. and Europe
- Exploring avenues for harmonization of study designs and timelines for pediatric plans across U.S. and European regulatory agencies
- Using multi-stakeholder guidance to develop a mechanism to prioritize drugs and drug classes for trials in children with CKD
- Optimizing planning of pediatric drug trials
- Identifying key considerations for a balanced assessment of perceived benefits and risks (including toxicity) with experts, patients, and caregivers.

Dr. Gipson discussed outcomes from the Kidney-PATCH group, noting that in the past, key opinion leaders communicated only with industry. This approach was not very effective, especially for pediatrics. Moreover, it did not include regulators, patients, caregivers, clinicians, or scientists.

Dr. Gipson cited the NephCure Kidney International (NKI) Gateway Initiative: Pediatric Inclusion in Glomerular Disease Trials Work Group as a third example of a community awareness model championed by a patient advocacy group. Members of this NKI Work Group include an impressive list of distinguished participants, including international members. This Work Group identified and prioritized barriers to inclusion of children in clinical trials. Work Group members also offered potential solutions to overcoming those barriers.

Prioritized barriers:

- The common misconception that inclusion of children in clinical trials is difficult from a regulatory perspective
- Lack of awareness of trial opportunities among patients and families
- Site burden in conducting trials in pediatric nephrology practices.

Proposed solutions:

- Clarify industry attitudes/barriers regarding inclusion of pediatric patients in trials
- Develop and disseminate a publication that discusses the regulatory pathways for inclusion of children in rare disease clinical trials
- Encourage and support patient and family engagement; collaborate with patient advocates to facilitate community awareness
- Promote site readiness
- Define, develop, and validate endpoints and trial designs fit for pediatric inclusion.

Dr. Gipson discussed glomerular disease, noting that more than 40 percent of those diagnosed with the disease are less than 18 years old. She pointed out that if that percent of patients is excluded from clinical study participation, the study is likely to fail. It is critical to include children affected by the disease to get meaningful outcomes. Only 3 of 10 current clinical studies of glomerular disease include children.

Dr. Gipson emphasized that waiting for results from adult studies is a significant barrier. In many cases, there will be no adult study results because these are orphan diseases, thus, creating the need for an orphan exemption waiver. Dr. Gipson noted that in November 2018, a multi-stakeholder group meeting was held to determine how to better deal with these issues and ensure that pediatric trials go forward. Since November, three industry sponsors have indicated they will include adolescents in their drug development study protocols. Also, this Work Group has taken on responsibility for developing a template for a pediatric inclusion dossier.

Dr. Gipson stressed that it is critical to not just include children in trials but include them early. She also emphasized that community organization and support is critical, and it must not be confined to only one organization.

Dr. Gipson concluded by delineating a number of key factors to consider in moving forward in pediatric drug development:

- Regulatory endorsement of pediatric needs and pathways
- Programs for safe collaboration
- Data needs to support progress
- Natural history
- Outcomes fit for purpose
- Documentation for community use, which becomes part of a public resource.

Questions and Answers
Submitted from attendees and webinar participants

Question 1: From Dr. Tracy King. She pointed out that a lot of the work that her office is working on focuses on rare diseases. She noted that much of what PTN is doing is a fit with that work, and that there seems to be a possible opportunity for collaboration.

(a) Has the PTN done studies of rare diseases?

(b) Do you think that would be a fit for your network?

Response: Dr. Benjamin and Dr. Zimmerman. Yes, the PTN has conducted studies of rare diseases, including pediatric cardiac conditions, renal transplantation, and blood pressure. These studies have resulted in a few different labeling changes. This is something that could continue to be addressed in the future to some extent. The PTN is often asked about biologic studies and orphan drug indications. However, moving forward, the focus for the mechanism remains on off-patent therapeutics.

Question 2: From Ms. Agoratus. If adalimumab is approved for Crohn's Disease, but not for UC, what happens in pediatric cases of IBD of unknown etiology?

Response: Dr. Altepeter. Dr. Altepeter noted that there are currently no programs being developed for IBS, mainly because that diagnosis is made in young children before their phenotype is fully clarified. She explained that sometimes undifferentiated IBD is diagnosed in the youngest children because it is not yet known which of the two pathways they will go down. It should be noted that it is typically not expected to be the ultimate diagnosis and will change as the child ages and the disease progresses.

Question 3: From webinar participant: There seems to be limited efforts from investigators to do clinical trials, possibly because of limited acknowledgment of their work from within their own institutions and also due to the significant cost involved in conducting these studies. How do you encourage academic department chairs to incentivize their staff to do these kinds of studies?

Response: Dr. Benjamin. There are several issues involved. There is general acceptance that this is a system problem unique to schools of medicine, over which PTN has very limited, if any, control. He argued that if Duke University is capable of determining an equitable way to reward/promote investigators for their collaborative research, then that model should apply to other universities. Dr. Benjamin did note that it takes local effort on how to award people for large scale clinical research.

He also emphasized that mid- and junior investigators, as well as trainees, play a critical role—they are the individuals who are responsible for enrolling study subjects. Without their efforts, it is likely that not enough subjects would be enrolled. If not enough subjects are enrolled, the study cannot be conducted. Dr. Benjamin noted that the PTN has only two committees: the first to determine if the study is going to be conducted. The second committee deals with the acknowledgment/access journal masthead. He noted that the PTN has developed a "boilerplate" template that links contributors directly to the masthead. He also pointed out that the study team that conducted the trial is acknowledged on the masthead. The PTN executive leadership does not control the masthead. Dr. Benjamin also noted that for secondary manuscripts, the intent is to reward and acknowledge those

individuals who were leading enrollment; trainees are acknowledged. He explained that the PTN tries to make financial compensation as equitable as possible, matching level of effort with financial benefit. Dr. Benjamin further noted that determining how to acknowledge voluntary work is a somewhat complicated issue, as well.

Question 4: From Dr. Kaelber: Could there be biases regarding selection and data collection? Also, could there be biases regarding site selection that could influence outcomes? Are the study sites representative of the entire patient population?

Response: Dr. Alexander. Much of what BPCA and NICHD do relies on multi-centered trials that are studying several diseases at several sites, for example, out-patient clinics, hospitals, or large tertiary care centers. He also noted that FDA often receives a considerable number of questions regarding how/when different hospital systems influence how/where an individual is actually being treated.

Question 5: From webinar participant. What is the use of trial designs such as platform trials to determine feasibility/methodology in conducting pediatric research?

Response: Dr. Zimmerman. Multi-drug protocols and platform trials benefit in having groups of investigators conduct certain studies with the same outcomes.
Dr. Reaman emphasized that the efficiency from master protocols and platform trials, especially trials dealing with rare and/or life-threatening diseases, can't be understated. He agreed that evaluation of drug use of master protocols and platform trials is clearly developed and supported in certain instances, especially when there are requirements for enriching the population being studied. He also emphasized that outcomes from these types of studies, if robust, could lead to increased enrollments. He agreed that certainly for oncology, platform trials are the way to go.

Dr. Gipson pointed out that the structure of a platform trial is anchored on a common IRB and a master service agreement. She also pointed to the increased interest in the United States in studying rare diseases. Dr. Gipson cautioned that multi-site trials such as these involve many different investigators, which in turn require increased additional effort from the research site regarding administering the study. She pointed out there is the potential to lose the initial focus of the study and conduct. At the same time, she emphasized that these study designs present an increased opportunity for various groups to get involved.
Dr. Reaman also noted that in the traditional (old) model, study activity was not assessed until phase 2. The new approach could save time and valuable resources.

Question 6: From Dr. King. The PTN focus is on off-patent agents. What is the best way for investigators to advocate for new orphan drugs or get approval to study on-patent agents, and get pediatric labeling for these agents?

Response: Dr. Benjamin explained that most drug developers typically have two organizational "arms": 1) a pre-market approval arm, which drives the first indication for expanding the label; and 2) a post-marketing "arm," with an investigator-initiated trial that may /may not result in label change. When approaching a potential developer, the investigator needs to be able to argue that this idea will speed up the drug approval process and that it does not require a pilot study that has to do with the first indication.

Dr. Benjamin offered some other potential approaches:

- Follow FDA Orphan Drug Program. He emphasized that this is a very solid mechanism. Many of the meeting participants have experience with this mechanism and are familiar with this process.
- If the molecule has been labeled, and if it satisfies the PREA directive, there may be a way to get an extension from FDA.

Dr. Alexander also noted that a drug that is proven and already marketed as an orphan drug may offer opportunities for submitting a Written Request for an extension. Dr. Alexander discussed the example of a drug still in development, and not yet approved for any population. He noted that the FDA recognizes that there are additional hurdles that must be addressed. He pointed out that identifying ways to evaluate the drug in the pediatric population may be of value, especially when dealing with young children.

Dr. Benjamin also identified the National Center for Advancing Translational Sciences (NCATS), specifically the NCATS Trial Innovation Network as a potential funding source.

Question 7: From Dr. Kelly. He asked about diseases that are not orphan diseases, such as pediatric obesity. He noted that there are many on-patent drugs that companies are slow in doing their studies. Is there a way to encourage drug developers to initiate their trials sooner? Does the PTN/BPCA have a role in expediting this process?

Response: Dr. Benjamin explained that this is a business decision. In this situation, the PTN has no role. However, the second issue is whether or not the PTN itself can do the study through the BPCA mechanism if the molecule is not off-patent. He suggested the investigator might want to consider including a study design that addresses validating end points or biomarkers, or inclusion/exclusion criteria, or that would enhance children's health.

NIH BPCA and Our Role in Identifying and Addressing Challenges in Pediatric Drug Development and Therapeutics

Perdita Taylor-Zapata, M.D.

Dr. Perdita-Taylor opened this session by directing attendees to the newly launched BPCA web site. She emphasized that the new web site has been designed to be more interactive and will serve as a repository for the most current information on BPCA program activities with links to other relevant programs and information.

She explained that this discussion would continue the morning's presentation and elaborated on how the BPCA program mission fits organizationally, not only as a component within NICHD, but also within the NIH overall mission and goals. Dr. Taylor-Zapata also pointed out that the hope is that BPCA will continue as a bridge, not only internally within NIH and FDA, but also as a bridge to academia and potentially to industry, even though the program focus is on off-patent therapeutics. Despite considerable challenges and a steep learning curve, Dr. Taylor-Zapata pointed out that since the BCPA was launched in 2002, there also has been significant success in meeting their mandate—notably achieving labeling changes without drug developers' direct involvement.

Dr. Taylor-Zapata explained that the program initially looked at individual drugs, supporting legacy trials with individual academic centers to study a specific drug. She explained that the program then moved to a therapeutic focus with establishment of the PTN in 2010.

Dr. Taylor-Zapata explained that the BPCA program has other functions, including co-funding drug development programs with other Institutes that have other networks, as well as co-sponsoring workshops with other organizations—all with the goal of moving pediatric drug development forward. She noted that in looking toward the future, BPCA is exploring ways to further incorporate lessons learned, as well as engaging more stakeholders in the process and being more productive in those collaborations. While the BPCA program has made significant achievements, Dr. Taylor-Zapata emphasized that within the next 3 to 5 years, BPCA needs to do a better job of making the stakeholder community and general public aware of those achievements, as well as the expertise and knowledge resident within the program.

Dr. Taylor-Zapata reiterated that the program continues to focus on drug development. She referred to the definition of the drug development process attributed to Dr. Robert Bell, noting that the goal of this process is to "…find a drug that promotes health and modifies disease." She also noted that this is a painstaking process, one that can take 20 years and that can cost millions of dollars.

The issue is how to do drug development well and do it effectively. Dr. Taylor-Zapata noted that with BPCA and PREA, there have been considerable advances, but there is still much to do in drug development, especially how to incorporate special pediatric populations, such as children with rare diseases, as well as children with intellectual/developmental, physical, and mental disabilities, into these clinical trials. She explained that the BPCA program is already reaching out to form trans-NIH and trans-NICHD working groups to identify and galvanize an infrastructure that may already be in place within other networks.

Dr. Taylor-Zapata next reviewed key issues and challenges in pediatric drug development that had been described earlier, and highlighted certain examples, including:

- Efficacy. (Can data be extrapolated?)
- Frequent "off-label" use in pediatric populations: impacts on extrapolation
- Endpoints, including developmental trajectories
- Duration of follow-up.

She also reiterated that many issues discourage the testing of drugs in children, including:

- Lack of incentives
- Ethical issues involving parental permission and the child's assent
- Need for technology to provide means to monitor patients and test very small amounts of blood
- Possibility of unanticipated adverse reactions/toxicity
- Threat of effects on growth, development, or health long after drug administration

- Difficulty in predicting dose-response or concentration-response relationships by extrapolation from data obtained in adults
- Lack of a sustainable infrastructure to conduct pediatric pharmacology research.

Dr. Taylor-Zapata briefly described the differences in the general order and culture of drug development in adults compared with adults, noting that the mechanism of disease is different in children than in adults. She also summarized the gaps that continue in drug development, emphasizing that these gaps need to be closed:

- Long-term toxicity/safety
- Disease biomarkers/endpoints
- "Modeling/OMICS" (e.g., genomics, proteomics, or metabolomics)
- Formulations.

Dr. Taylor-Zapata explained that the BPCA is a non-funded mandate that relies on NIH Institutes and Centers (ICs) and Branches for support. She presented a list of those ICs that currently contribute to the BPCA program. She emphasized the importance of continually dialoguing with these organizations.

She next described the BPCA Clinical Program organizational structure and program components:

- PTN (Duke University)
- DCC
- T32 Training
- U54 Centers Program
- Logistics Support.

She reviewed the program workflow process that begins with prioritization based on input from stakeholders and potential developers, as well as outreach to NICHD, NIH, and FDA liaisons to generate an updated BPCA Annual Priority List, which is shared with the PTN. Dr. Taylor-Zapata summarized the process discussed earlier by Dr. Benjamin for PTN concept review; a protocol is then developed that flows to protocol finalization within the DCC. She noted that the proposed study protocol is reviewed with FDA during pre-Investigational New Drug (IND) Application meetings. She explained that these meetings are designed specifically to engage FDA early in the IND process. She noted that once a study is completed, a clinical study report is prepared for submission to FDA for potential label change; data are managed and posted on DASH.

Dr. Taylor-Zapata summarized the BPCA overall vision aimed at:

- Practical/feasible priority lists
- Better clinical trials
- Pharmacology-focused research
- Expanded workforce training.

Dr. Taylor-Zapata emphasized that the ultimate aim is to improve care through better labeling. She also emphasized the BPCA program's role as a source of pharmacology expertise and as a leader in innovative research/trial design and its efforts in pediatric regulatory research. She pointed to the BPCA program as a model of cost efficiency and in promoting investigator training. Dr. Taylor-Zapata encouraged participants and stakeholders to tap into these BPCA resources and expertise as the program moves forward in advancing its role as a bridge within and across the entire pediatric drug development program.

In addition to continuing its mandate to improve labeling, Dr. Taylor-Zapata briefly defined potential new territories for BPCA/PTN clinical trials, including:

- Conducting more trials; compiling more DASH records
- Improving NIH-wide collaborations for clinical, translational, and basic research related to pharmacology, particularly drug development for pediatrics
- Improving FDA collaborations with common areas of interest
- Sharing BPCA experience in single IRB implementation
- Expanding T32 training program and harmonizing U54 research areas
- Developing novel mechanisms for determining new priorities
- Developing clinical trials training programs
- Improving dissemination to all stakeholders.

Dr. Taylor-Zapata reiterated that in addition to clinical trials, the BPCA program co-funds a number of studies, as well as BPCA workshops and scientific collaborations. She also called participants' attention to an FDA Funding Opportunity Announcement (FOA) on "Development of Standard Core Clinical Outcomes Assessments (COAs) and Endpoints." The application deadline for this FOA is May 31, 2019.

In moving pediatric pharmacology forward while continuing to work within the realm of clinical trials, the BPCA program is also exploring other opportunities in areas such as basic science and early research, as well as clinical trials. Dr. Taylor-Zapata again emphasized the importance of developing and maintaining a centralized post-marketing data repository.

She closed her presentation by reiterating that the goal of the BPCA program is to get children to a state where they can be healthy and productive adults. She encouraged participants to submit their recommendations and inputs regarding potential future opportunities and areas warranting study within the BPCA mandate.

Pediatric Drug Development Priorities at NICHD

Rohan Hazra, M.D., Chief, Maternal and Pediatric Infectious Disease Branch; Acting Chief, OPPTB, NICHD/NIH

Dr. Hazra began by acknowledging Dr. Taylor-Zapata for her dedication and efforts in continually exploring ways to expand the BPCA program, and to increase awareness of the program across NIH as well as with external stakeholders.

Dr. Hazra noted that he would present a broad overview of current NICHD and NIH activities related to pediatrics, focusing on the following:

- NICHD Strategic Planning
- (N-PeRC)
- Pediatric antiretroviral drug development
- NICHD DASH

Dr. Hazra first explained that the NICHD strategic planning process has four key goals:

- Enable internal and external stakeholders to look at NICHD's portfolio with a fresh perspective
- Review and refocus NICHD's science
- Align resources with scientific priorities
- Improve the health of the populations we serve.

He pointed out that NICHD's reach extends to more than just children, and that the Institute serves pregnant women, neonates, infants, and teens, as well as individuals with disabilities. He also explained that under the 21st Century CURES Act, all NIH Institutes are to review and update their strategic plans. He also noted that the NICHD strategic plan had not been updated since 2000.

Currently, the Institute is moving ahead on an aggressive 15-month process scheduled to end by autumn 2019. He summarized key milestones in the process, beginning with pre-planning in January through April 2018, followed by data collection and analysis from January to August 2018. That phase was followed by seeking input and comments from external investigators and the public from September 2018 to February 2019. He noted that the responses from the Request for Information (RFI) issued by NICHD were considerable, and that these RFI responses are currently being reviewed and evaluated by internal NICHD teams.

Dr. Hazra emphasized the importance of eliciting and receiving input from investigators; they will actual carry out this work within the requirements and rubrics of the approved strategic plan. He also noted that between March and July 2019, plan details will be finalized, with the intent to communicate and implement a new, final plan by autumn 2019.

Dr. Hazra next reviewed the core principles that are the bedrock of the NICHD strategic planning vision, reiterating that this "organic" process applies to both intramural as well as extramural activities:

- Transparency
- Decisions informed by evidence
- Stakeholder participation, including junior and senior investigators, other agencies, patient advocates, and other community members.

Dr. Hazra pointed out that NICHD is often questioned about whether the return on investment for large studies is as cost-effective as the return from funding smaller, numerous Research Project Grant (R01) initiatives. He noted that there is no clear-cut answer, that it depends on how impact is measured. For example, he pointed out that the number of papers cited in influential guidelines would indicate that these networks are quite robust.

Dr. Hazra next summarized the draft research themes that were identified from the input received resulting from the RFI inviting public comment:

- Understanding early human development
- Setting the foundation for a healthy pregnancy and lifelong wellness
- Promoting gynecological, andrological, and reproductive health
- Identifying sensitive time periods to optimize health interventions
- Improving health during the transition from adolescence to adulthood
- Ensuring safe and effective therapeutics and devices.

He noted that more details about these research themes are available on the NICHD website. Dr. Hazra also explained that scientific priority areas ("warps"), compiled from investigator and public input, are "woven" into the strategic plan, cross-cutting with "wefts," those over-arching concepts that are embedded in all priority areas, such as:

- Inclusion of our populations
- Nutrition
- Health disparities
- Infectious diseases
- Global health.

Dr. Hazra explained that he would focus on Research Theme #6: Ensuring Safe and Effective Therapeutics and Devices. He reiterated that the goal of this research theme is to develop, test, and validate safe and effective therapeutics and devices, specifically for pregnant and lactating women, as well as for children and individuals with disabilities. He identified key scientific opportunities to potentially identify ways to design and conduct these studies in a more innovative and robust fashion:

- Consider and address the specific needs of pregnant and lactating women, children, and individuals with disabilities through their inclusion in the development, testing, and validation of therapeutics and devices.
- Evaluate medications, including safe and effective dosing, in these specific populations to allow for better management and treatment of common conditions.
- Utilize real-world data (e.g., EHRs, existing datasets, or other big data approaches) to discover potential adverse events, positive outcomes, or common comorbidities in these populations.
- Enable implementation efforts in health systems by supporting acceptability and adherence research to ensure that interventions can be meaningfully used in these populations to achieve the more expansive and hoped-for public health impact.

Dr. Hazra next discussed N-PeRC. He explained that the goal of the Consortium is to harmonize efforts in child health research across the 27 Institutes and Centers, almost all of which fund some aspects of child health research. He also noted that NICHD is the ninth largest Institute with a budget of $4 billion in FY 2018. Although NICHD is the largest funder of pediatric drug and device development, it contributes only 18 percent of the overall funds for pediatric research funds at NIH, further underscoring the need for forming collaborations with both external and internal stakeholder partners.

Dr. Hazra explained that during bi-monthly meetings, N-PeRC members discuss how to better identify gaps, as well as opportunities for NIH-wide collaboration, focusing on the Consortium's current priorities, including:

- Pediatric drugs and devices
- Data sharing
- Trans-NIH-supported training to grow pediatric workforce
- Transition from adolescence to adulthood.

He also noted that N-PeRC is also looking at ways to enhance communication between NIH and research advocacy organizations regarding current efforts dealing with these priorities. Another priority is to support outreach efforts to encourage senior pediatric researchers to serve on review panels, especially important given the lack of pediatric expertise in many study sections. He also referred to the NIH Center for Scientific Review (CSR) as a potential internal collaborator.

Dr. Hazra next discussed current research studies in pediatric antiretroviral drug development. He referred to the results of a study published in the *New England Journal of Medicine* during 2010 and 2012. This study found that lopinavir/ritonavir was superior to nevirapine as part of initial treatment in infants with HIV. He explained that these results addressed PK, safety, and efficacy in a large, randomized clinical trial. He also noted that lopinavir/ritonavir was approved by the FDA and was recommended by the World Health Organization (WHO) for first-line treatment of HIV worldwide.

Dr. Hazra explained that although nevirapine continued to be used as part of initial treatment in infants, there were no significant changes based on those findings. However, treatment for adults has moved several generations ahead, including looking at new classes of drugs.

Dr. Hazra noted that pediatric drug researchers recognized the need to speed up pediatric drug development by optimizing research. He described the Paediatric Antiretroviral Working Group (PAWG). Formed within WHO, the PAWG Working Group includes members from WHO; FDA; the European Medicines Agency (EMA); and NIH. The Working Group also includes representatives from the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network, the NIH-funded pediatric HIV clinical trials group, as well as participants from PENTA, the European equivalent of the clinical trials group; the nongovernmental group, Drugs for Neglected Diseases Initiatives (DNDi); and the Children's Healthcare Access Initiative (CHAI) among others.

He referred to a 2017 paper, in which PAWG members recommended several actions to close the loop on pediatric development plans, including:

- Simultaneous enrollment of different age cohorts
- WHO weight band dosing
- Optimize use of PK data and modelling
- Alternative study designs
- Acceptability and feasibility.

Dr. Hazra reiterated that the vision of the PAWG founder, Martina Penazzato, M.D., is to create and sustain a partnership with regulatory authorities, industry, and researchers to work together to prepare better pediatric development plans that can be completed and approved more quickly. PAWG members would provide technical opinions on pediatric investigation plan/pediatric study plans (PIPs)/PSPs) to promote further across-agency focus and alignment. Dr. Hazra pointed out that the EMA has already offered to review PIPs when they are received.

Dr. Hazra next summarized several key FDA recommendations for guidance to industry in developing drugs for treatment of pediatric HIV infection:

- Include adolescents (12-<18 years of age) in adult phase 3 studies.
- Initiate pediatric formulation development immediately after adult phase 2 studies
- Conduct parallel enrollment of children 4 weeks to <12 years of age
- Include neonatal studies after dose established in older infants/children
- Follow weight band dosing aligned with WHO
- Conduct relative bioavailability studies
- Engage in early discussions with WHO and with non-governmental organizations (NGOs), as well as with FDA.

Dr. Hazra emphasized that the next step is to take what has been learned from HIV studies and apply those lessons to all pediatric therapeutics. He described the Global Accelerator for Paediatric Formulations (GAP-f) model created by Dr. Penazzato, discussed in an article in the *Journal of the International AIDS Society*. The aim of GAP-f is to shorten the decade-long gap between adult and pediatric drug formulations. This new framework is based on the HIV experience in low- and middle-income countries, with a vision of a cohesive approach among all relevant stakeholders.

Dr. Hazra next discussed NICHD's DASH. This centralized resource aims to accelerate scientific findings and improve human health by providing a repository for researchers to store and access de-identified data from studies supported by NICHD. Launched in August 2015 and governed by the NICHD DASH Committee, DASH can help investigators meet NIH data-sharing requirements for their own studies. It also can help investigators locate data from other studies for secondary analyses.

When it was launched, DASH housed eight data sets. Currently, DASH maintains 120 data sets covering 30 study topics. Of those 120 data sets, 19 are from BCPA-sponsored studies. Dr.

Hazra commended the BPCA DCC for its efforts in packaging and incorporating data into DASH as quickly as possible. Dr. Hazra emphasized the usefulness of DASH as a resource for junior investigators and trainees. He also noted that in less than 4 years, a total of 11 publications have emanated from secondary analyses of DASH-stored data. He acknowledged current NICHD Director, Diana Bianchi, M.D., and former Director Alan Guttmacher, M.D., for their support in conceptualizing and sponsoring DASH.

Dr. Hazra pointed out that DASH has added a new function—managing requests for NICHD biospecimens. He also noted that while itself not a biorepository, DASH serves as a portal for access to biospecimens associated with DASH data collections. He explained that investigators worldwide can now request both biospecimens and data for secondary analyses. Other than covering the costs of preparing and shipping biospecimens, these specimens are free of charge to investigators. Programs with biospecimens currently available include:

- Genomic and Proteomic Network for Preterm Birth Research (GPN) – three studies
- NICHD International Site Development Initiative (NISDI) – four studies
- Mothers and Infants Cohort Study (MICS).

Dr. Hazra concluded by noting that study topics involving biospecimens include AIDS, pregnancy, and preterm labor and birth. He also noted that the complex and logistically challenging issues have been addressed, and that the DASH biospecimen component will continue to expand.

Live Chat: Determining New Priorities for the BPCA Program

Facilitated by: Perdita Taylor-Zapata, M.D.
Christoph Hornik, M.D., Assistant Professor of Pediatrics, Department of Pediatrics, Duke Clinical Research Institute, Pediatric Trials Network, Duke University Medical Center

Dr. Taylor-Zapata explained that during this part of the meeting, participants were encouraged to share their comments regarding the state of current pediatric drug development research, as well offer their recommendations for possible topics for future studies. She also noted that **Dr. Walson** and Dr. Hornik would be available on line to respond to questions/comments regarding the PTN and data-related questions from the participants.

Dr. Taylor-Zapata also pointed out that this meeting, with the "Live Chat" session is only one means of information exchange. She explained that a follow-up electronic notice would be distributed from the BPCA program by mid-May.

Dr. Taylor-Zapata introduced **Dr. Kelly**, who had offered questions earlier in the meeting regarding obesity as a research topic. Dr. Kelly emphasized the importance of obesity as a public health issue and recommended that the BPCA program consider severe pediatric obesity as a priority that warrants future study.

Dr. Kelly emphasized that obesity has finally been recognized as a disease. Until fairly recently, severe obesity has largely been ignored, more than likely due to the social stigma attached to obesity. He noted that obesity is one of the most prevalent diseases in childhood; one out of

every three children between the ages of 2 and 19 are overweight. Significant morbidity is associated with severe pediatric obesity, which is also tied to other chronic and severe diseases.

Dr. Kelly pointed to the large obesity treatment gap. He noted that current treatment usually is focused on lifestyle modification, which is not generally successful, especially for severe pediatric obesity. The next treatment option is surgery, which is extreme. Dr. Kelly offered that pharmacotherapy is a logical next step. However, he explained that few obesity medications have been approved for patients older than age 16, and none have been approved based on pediatric clinical trials.

Dr. Hazra asked Dr. Kelly for his opinion of why pediatric obesity trials are not occurring. Dr. Kelly explained that this is a risky and sensitive topic for the pharmaceutical industry. Obesity oftentimes continues to be viewed as an individual, personal failure. The stigma of obesity has been pervasive, not just within the general public, but also within industry. Dr. Kelly also suggested that there likely is a concern within industry that conducting pediatric studies could possibly jeopardize or complicate adult studies. He further noted that industry may conclude that the return on investment for developing obesity pharmaceutics as prohibitive, even for adults.

Dr. Ward remarked that an overarching theme is emerging, one that crosses all therapeutic fields. He emphasized that there is a need to publicize pediatric clinical trials, underscoring the imperative not only to involve children and parents in participating in pediatric studies, but also to involve them in the study design up front. He also suggested that NICHD has an implicit obligation to disseminate information on the amount of off-label prescribing that currently occurs. Dr. Ward further urged that families should be motivated and enthused about having a critical role in design and conduct of these studies. Information on these studies should be disseminated in both print and online publications that target parents of pediatric patients.

Dr. Yao offered comments on the role of NIH BPCA in obesity studies. She cited several drugs that have been approved for treating obesity in adults. She explained that under PREA, the sponsors of these drugs are required to study them in children. She cautioned against expending public funds for studies that are already required under other legislation, such as PREA. Dr. Yao also agreed that there is more that can be done to include children early in these studies, and yet, not delay these studies. She also pointed to the need to require sponsors to involve children early on to minimize the period of off-label use.

Dr. Kelly thanked Dr. Yao for her comments, noting that a major frustration for investigators and patient advocacy groups, as well as for parents, is the prolonged time it takes to initiate these studies, especially studies involving children.

Dr. Leeder discussed the need for studying obesity as part of type 2 diabetes clinical trials. He noted that searches of the literature clearly pointed to the lack of studies of type 2 diabetes in children. He directed participants to a study, published in 2017, which identified several key issues. He argued that the study question is not really determining the correct or optimal dose, noting that when investigators reviewed PK studies, doses were extremely varied. He also pointed out that were no measures of exposure, making it even more difficult to define what is the response. Dr. Leeder reiterated that a clinical trial has a finite beginning and an end;

therefore, it is extremely important to determine the relation between exposure and response as early as possible. He acknowledged that numerous challenges are inherent in these studies. One of the major challenges is trying to assess the effect of long-term consequences. Without determining the normal progression of the disease, it impossible to assess the impact of the intervention.

Dr. Taylor-Zapata asked Dr. Hornik to comment on the work that the PTN has been doing regarding PK dosing and obesity. Dr. Hornik explained that while the PTN has studied drugs that are administered to obese children, it has not conducted studies of a specific drug focused on promoting weight loss in children. In conducting PK studies of children, including obese children, he explained that these studies focused on identifying the right dosing regimen that would be required for obese populations. Dr. Hornik explained that there are instances where researchers can fairly accurately predict that the PK in an obese child will differ from a non-obese child. In many instances, however, this prediction has proved to be untrue. Dr. Hornik pointed out that this result has been due to the dosing regimen in both obese and non-obese children, based on oversimplifying that fixed dose "cap" based on weight, depending on the age of the patient. He pointed out the potential impact of how PK data in children can affect the label. That is, if not deviating from a weight-based regimen, there may be no need to update the label, even if just confirming the dosing levels on the current label.

Dr. Hornik mentioned that there have been several discussions regarding studying the PK of several drugs. He emphasized that even if the PK in children is different than in adults, there may be no impact on the dosage for children. He also pointed out that much has been learned regarding the feasibility of drug studies in obese children. He also discussed the issue of the stigma of obesity in enrolling pediatric subjects. Dr. Hornik also explained that the PTN has focused on identifying drugs that are off patent and fall within the BPCA mandate.

Dr. Taylor-Zapata asked **Dr. Sullivan** to discuss the issue of dosing drugs in obese patients. Dr. Sullivan explained that her group has been focusing on identifying gaps in research in obesity. She explained that they just received approval of their initial concept and authorization from the American Academy of Pediatrics to proceed. She noted that they will be working on finalizing the concept paper, co-authored by Dr. Zimmerman, during the next few months.

Dr. Taylor-Zapata also asked Dr. Walson to discuss PREA compliance.

Dr. Walson suggested that FDA clarification regarding PREA compliance would be helpful. Dr. Alexander pointed out that currently there are no penalties for industry non-compliance, other than being placed on a non-compliance list. That list does have some impact within and across industry. However, currently there is no governmental repercussion or penalty for non-compliance. He also explained that because of the inherent complexities associated with pediatric drug studies, industry often makes the case for the need to extend study deadlines to complete the trials. The emphasis continues to be on addressing the pressing need to get studies enrolled, get protocols in place and approved sooner, to get studies accomplished sooner, and get protocols approved quicker.

Dr. Alexander also pointed out that industry sponsors face a host of issues in study design, often resulting in FDA being asked to defer the due date for their studies. Dr. Alexander explained that FDA is trying to streamline some of this process by encouraging collaboration among industry and these advocacy groups, and by trying to expedite the process. They still face the issue of not clearly understanding the disease path. He also reiterated that it still unclear why it is so difficult to get these studies done and getting patients involved early on.

Dr. Walson urged that obesity advocacy groups and the pharmaceutical industry need to be involved early in the process. He suggested that there is a "disconnect" between the two groups that has to be resolved. Dr. Walson also pointed out that oftentimes the pharmaceutical industry argues that they can't do obesity studies, chiefly because they have problems enrolling study subjects. At the same time, parent groups say they want to get their children enrolled in these studies but have difficulty in locating them. Dr. Alexander agreed that the process would definitely benefit from collaboration among the drug sponsors with PREA requirements and parent advocacy groups. He explained that FDA should definitely encourage dialogue among these groups.

Dr. Yao pointed out that since 2007, there were 803 studies under PREA that were outstanding. Of those, almost 2/3 hadn't yet reached their due dates. She acknowledged that there has been little success in getting studies completed quickly, once a drug has been approved. Dr. Yao suggested that some of these delays have been due to sponsors having problems with feasibility and in enrolling and recruiting subjects. She also pointed out, however, that at the same time, while we hear much about the epidemic of type 2 diabetes and the obesity epidemic, industry sponsors still are unable to enroll subjects in these studies. Dr. Yao noted that the FDA has been working with industry sponsors, as well as the academic and treating communities to solicit their input in resolving problems to get studies completed quicker. Dr. Yao noted that among academic researchers, there has been acknowledgment that these type 2 diabetes studies are difficult to complete. FDA has built on those findings to change study design.

Dr. Yao recommended that NICHD and BPCA support FDA efforts by searching databases for "lessons learned" from earlier studies that also had difficulty in enrolling patients. She also suggested that study designers contact the FDA for assistance in pressuring the industry to be more aggressive in enrolling subjects and completing these studies.

Dr. Kelly concurred, but also wanted to emphasize the distinction between studies of type 2 diabetes in adolescence, which are exceedingly difficult to enroll, and pediatric obesity studies. He underscored that it is definitely feasible to enroll obese children in these studies. He pointed out that his organization has multiple R01's in place, with little or no problem in enrolling subjects. Dr. Kelly argued that industry may be using the feasibility issue as a defense for not moving ahead on enrolling study subjects.

Dr. Walson noted that BPCA is for off-patent drugs. He reminded participants that studying off-patent drugs that might benefit children should be a priority for the group.

Dr. Gipson referred to the model adapted by her professional society. She noted that this group has expertise and is willing to be included in all stages of a clinical trial— from feasibility to

study design, to conducting the trial. She suggested that relying on groups like this with expertise in study design may be a useful model for others to consider. She also noted that the technologies and tools available in the current electronic era make cross-organization clinical trials much more feasible than they have been in the past.

Dr. Gipson also described another example in the international context where a pediatric drug development plan is due at the same time the drug development plan is due for adults. She offered that a simple solution would be to involve plans for a pediatric trial in the original plans for adult research, thus expediting the overall process.

Dr. Kaelber asked if there should be a priority around methodology, especially, the use of EHRs. He noted that many of these drugs are already being used off-label with children, as documented in EHRs. In effect, these studies are already going on. He offered that there should be a way to leverage these "studies" while recognizing that they would not hold up to the scrutiny or rigors of a traditional prospective trial. Dr. Kaelber also noted the need to differentiate between clinical data and clinical evidence and how to bridge that gap.

Dr. Kaelber noted that "big" data from EHRs are becoming increasingly available, especially in adults. He mentioned that a number of studies are using "drug reconditioning" that looks at EHR data to identify the effect of a drug (most likely, FDA-approved) that is the focus of the study, but also to anecdotally note if the drug being studied has a positive side effect. Dr. Kaelber suggested that this approach might warrant consideration, although he acknowledged that the situation is more complex when dealing with the pediatric population.

Dr. Sullivan emphasized the need to be cautious about how EHR data are used. He agreed that this is a good place to start and that there definitely is value in EHRs. It also is important to carefully determine how to better use EHR data.

Dr. Kaelber pointed out that methodological development is key because EHR data are "messier" than research data. He noted that researchers need to be careful not to "throw the baby out with the bath water." He suggested allocating resources to better determine how to use EHRs, including identifying those questions that EHRs will be good at answering and those questions that EHRs will not be good at addressing.

Dr. Taylor-Zapata pointed out that this conversation already has begun within BPCA and PTN. She also noted that when the BPCA program was first launched in 2004/2005, staff looked at databases and EHRs, hoping to be able to link the two systems. They found that it was not possible to link these systems at that time. However, 15 years later, some of the technological advances that have been made since 2005 make some of those impossibilities achievable. Dr. Taylor-Zapata referred to a small pilot study that will be conducted within the PTN that will look at how to harmonize EHR data systems within the Network.

Dr. Hornik explained that an EHR is a powerful source of data with a tremendous amount of potential. At the same time, there is still much methodological work to be done regarding how best to harness these data. Up to now, the PTN has focused on two areas: (1) implementation of a shared data model at the front end of getting data into a centralized system that can be used in

future research and (2) identification of how to analyze these data. Dr. Hornik pointed out that even with the most advanced technologies, there is considerable work to be done, beginning with extrapolating data from various sites to a common shared system. He explained that to date, the PTN has not had much success in developing a shared data model. Mapping data from several sites has turned out to be a huge undertaking, involving some of this meeting's participants.

Dr. Hornik also explained that investigators are just now trying to determine how best to leverage that shared data model. He noted that the PTN is now pursuing a revised strategy that represents a new way of thinking, more like a distributed model. He further explained that with this model, the PTN would function as a coordinating center, sharing tools with the sites to help map and extract data. Dr. Horik noted that this is a much more cautious step-by-step approach, with investigators validating data within the context of a prospective clinical trial, assessing one variable at a time. He explained that this approach will hopefully result in a more accommodative model that is much more workable than the previous approach.
He also pointed out that there is still an opportunity to leverage these data elements, given the considerable amounts of data from the PTN and from a previous collaboration with the Pediatric Medical Group, which the PTN is happy to share to answer methodological questions.

Question (from Dr. Mulugeta), who asked if there is any consensus in the pediatric medical community regarding efficacy bench marks for obesity pharmacotherapy.

Response (Dr. Kelly): He explained that currently there is little, if any, consensus on efficacy benchmarks for obesity drugs, even for adults. He noted that the FDA looks for a 3-5 percent weight loss in adults, but the situation is different with children, depending on age. Dr. Kelly also explained that his team set a 5 percent body mass index, (BMI) reduction benchmark. He cautioned, however, that investigators need to know the anticipated dose levels, as well as what medications are available and/or are off-label. There is also a need for pediatric trials in relation to risk/benefit balance. That is, what is the amount of weight loss and BMI that we should setting as goals? Dr. Kelly emphasized that these questions and issues provide even more rationale for doing these pediatric obesity trials.

Dr. Gipson noted that nephrology has had low representation on the BPCA priority list with no specific drugs being recommended for review. She offered to identify a high-priority list of off-patent drugs that could be studied and to help accurately assess information received.

Dr. Taylor-Zapata explained that there is a form being developed as part of the BPCA program to solicit nominations for the 2020 Priority List. This form will enable participants to submit their suggestions and potential concepts for consideration. She will send that information to participants and to all BPCA stakeholders to solicit their input.

Dr. Hazra reiterated that drug and device development in children will be a major priority addressed in the NICHD strategic plan. He urged participants to go beyond the BPCA program and think in broader terms, across NICHD and NIH. He noted that in current HIV studies, NIH investigators are working with academicians and with industry. He suggested adapting that approach to identify topics for the BCPA priority list.

Dr. Taylor-Zapata emphasized that these are global issues. She pointed out that given Dr. Hazra's multiple roles, he is a great resource for fostering the sharing of BPCA information and discussion of the BPCA mandate with internal, as well as global external, stakeholders.

Question: from Dr. Purucker (read by Dr. Taylor-Zapata, who asked if the common data model (CDM) is to be applied to EHR data exported for use in research, or are providers to enter information into the EHR using standard format?
Response (Dr. Hornik): In responding to the questions, Dr. Hornik noted that he presumed that the question was whether the CDM had to be implemented at time of data entry or if it was based on data extraction from the EHR. He explained that EHR data fields had to be mapped to a model designed by the DCRI based on the PedsNet model.

Adjournment

Dr. Taylor-Zapata thanked presenters, as well as in-person and webinar attendees for a productive and insightful meeting. She adjourned the meeting and directed participants' attention to a projected slide with contact information for the BCPA program.