

Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
Best Pharmaceuticals for Children Act (BPCA)
2016 Annual Stakeholders Meeting
December 8, 2016
6710B Rockledge Drive, Room 1427
Rockville, 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 was open to the public, and included invitees representing organizations including, but not limited to, academia, NIH Institutes and Centers, the U.S. Food and Drug Administration (FDA), the pharmaceutical industry, and members of pediatric advocacy groups.

Welcome and Overview

Perdita Taylor-Zapata, M.D. Medical Officer, 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, but would focus on providing participants with information and applicable knowledge relevant to individual stakeholders. She noted that the goal was for participants to be informed about the uniqueness of the NIH BPCA program. Dr. Taylor-Zapata also emphasized that presenters would describe some of the challenges faced and share lessons learned, but also share how they leveraged these challenges into successes.

Dr. Taylor-Zapata pointed out that presenters would offer their individual perspectives of the BPCA program and its role in pediatric drug development. She briefly described the five-step NIH BPCA review process:

- Prioritization
- Written Request (WR)/Proposed Pediatric Study Request (PPSR)
- Clinical Trial
- Data Submitted to the FDA
- Label Change

Dr. Taylor-Zapata explained that this process is often challenging, and always complicated. While the ultimate goal is to effect a label change in a particular medication, the process also looks at overarching issues, such as endpoints and outcome measures, how to better maximize recruitment/retention in pediatric clinical trials, drug formulation, how to train the next generation to continue and further engage in the study of pediatric pharmacology, and how to deal with adverse events (AEs) and toxicity in pediatric populations. Dr. Taylor-Zapata concluded by emphasizing that while these are significant challenges, success is still possible and that will be highlighted today.

She also asked that remote meeting participants use the webinar chat function to submit questions. She also urged participants to complete the evaluation form, pointing out that OPPTB values this input, and uses attendee comments and suggestions to shape and inform the structure and content of future BCPA program meetings.

BPCA Program in a Nutshell: From Then to Now and Beyond

Anne Zajicek, Pharm.D., M.D., Branch Chief, OPPTB, NICHD, NIH

Dr. Zajicek began her presentation by reiterating the purpose of the meeting as an opportunity for participants to interact and engage in dialogue regarding the BPCA program. She explained that the legislative mandate of the BPCA is to improve pediatric labeling. To fulfill that mandate, NICHD's programmatic goal is to improve/increase the information/evidence available to determine the best/most rational way to use a specific medication to treat children. Dr. Zajicek emphasized the need for clinical trials that accurately and precisely report information so that study findings can be verified and translated into sound clinical practice and treatments for children.

She reviewed the FDA Good Clinical Practice Guidance for Industry:

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

<http://www.fda.gov/Drugs>

Dr. Zajicek next presented a summary of the NIH-mandated protocol for identifying therapeutic areas for clinical trials, including considerations for prioritizing:

- Therapeutic gaps
- Potential health benefits of research
- Adequacy of required infrastructure
- Neonates (since 2012)

She also expanded on the five-step prioritization process that Dr. Taylor-Zapata described earlier:

- Public outreach to stakeholders for therapeutic areas/drugs
- Scoring by volunteer stakeholders
- Input from NIH liaisons and FDA
- Final NICHD review
- Final annual BPCA Priority List to the *Federal Register*

She presented several examples of ongoing involvement of other NIH Institutes and Centers (ICs) in the BCPA, including the National Heart Lung and Blood Institute (NHLBI), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the NIH Library. Dr. Zajicek also pointed out that the National Institute of General Medical Sciences (NIGMS) is actively involved in supporting

the T32 clinical pharmacology training program and that in addition to a number of product studies, the National Cancer Institute (NCI) is actively involved in the BPCA Pediatric Oncology Working Group (WG).

Dr. Zajicek next described the process for initiating clinical trials in the BPCA Program:

- Prioritization: input from stakeholders, NICHD, NIH, and FDA, resulting in the BPCA Annual Priority List, published in the *Federal Register*
- Prioritized drugs of interest are then placed in the Pediatric Trials Network (PTN) Opportunistic Protocol: which provides limited PK/Safety data in an effort to develop a template for future/larger PK, safety and/or efficacy studies
- Once a study moves forward into full implementation, a Meeting Request is developed: study protocol is formalized, request for pre-Investigational New Drug (IND) Application meeting with FDA, regulatory package from the Data Coordinating Center (DCC) submitted to FDA for review
- FDA responds to questions and adds comments on study design, endpoints for final study implementation.

She also described additional details into the components of the clinical trial process that lead to label change:

- PTN: protocol finalization, study site subcontracts, study performance, and site performance
- DCC: Data Management Center (DMC) oversight, clinical data quality review including site audits, Clinical Study Report (CSR) finalized once study is complete and data are submitted to FDA, IND meeting request
- FDA: review of data, site audits, ready-to-file determination, docket number assigned
- DCC: submits de-identified clinical trial data as PDF to docket
- FDA: label determination.

Dr. Zajicek reviewed labeling progress that has been made under the BPCA, including new labels and document submissions, and products with docket numbers expected, as well as other labels expected within the next year.

She next discussed the key components of the BPCA program infrastructure:

- T32 Training: developed to address the critical shortage of pediatricians trained to conduct pediatric clinical trials; NICHD and NIGMS
- U54 Centers Program: currently implementing second iteration; Children's National Medical Center (CNMC), Indiana University, State University of New York (SUNY) Downstate, University of California, San Diego (UCSD)
- PTN (Duke University): Management, clinical pharmacology, pharmacometrics, safety and ethics, and devices
- DCC: regulatory submissions, statistical support, site monitoring/auditing.

Dr. Zajicek next elaborated on the purpose and focus of the Research in Pediatric Developmental Pharmacology (U54) program. She noted that U54 is intended to provide an arena for multidisciplinary interactions among basic and clinical scientists interested in establishing high-quality translational research programs in pediatric pharmacology, each of which focus on very different aspects of pharmacology.

CNMC: Pediatric Toxicity and Efficacy in Long-Term Systemic Treatment with Anti-Sense. This work monitored kidney toxicity through urine biomarkers and shed renal cells. Results indicated that restoration of dystrophin in animal models was dose dependent, and that higher doses resulted in significant and systemic increase in the skeletal muscle. Dr. Zajicek pointed out that the U54 team has been working with pharmaceutical companies in a “second generation” clinical trial design. She also noted that this study has been challenged with the issue of how to handle samples at clinical sites, resulting in development of videos to use in systematic training of sites for biopsy preparation, as well as standard operating procedures (SOPs) for testing.

SUNY Downstate Medical Center: Molecular and Clinical Pharmacology of Retinopathy of Prematurity (ROP). These studies in rats centered on advancing knowledge on the molecular and biochemical mechanism leading to ROP and identifying pharmacologic interventions to prevent ROP and lifelong blindness. Among the results of this study, Dr. Zajicek noted that researchers found that early caffeine and topical ketorolac, a non-steroidal anti-inflammatory drug (NSAID) exerts pharmacologic synergism and prevented development of severe Oxygen-Induced Retinopathy (OIR).

UCSD: Developmental and Translational Pharmacology of Pediatric Antimicrobial Therapy. This study had two overarching goals—(1) to bring together clinical and non-clinical experts in the fields of mental physiology, pharmacology, and infectious diseases to conduct translational research to advance pediatric developmental pharmacology, and (2) increase the mechanistic understanding of developmental pharmacology and host interactions with antimicrobial therapy. This work provided a comprehensive analysis of potential drug-drug interactions between leading pharmaceutical antibiotics and endogenous antimicrobial peptides (AMPs).

Indiana University. Dr. Zajicek also summarized the Indiana University program, which is aimed at discovering novel biomarkers that predict the efficacy and toxicity of chemotherapies for children with cancer, to lead to development of improved treatment strategies to optimize the use of anti-cancer chemotherapy in children. As examples, she described two studies, the first of which involved a clinical test site in Kenya. The second study, which looked for biomarkers of sinusoidal obstructive syndrome (SOS) in children undergoing Hematopoietic Cell Transplantation (HCT), underscored the need for reliable, noninvasive methods for diagnosis and prognosis of SOS early after HCT.

Dr. Zajicek next discussed several key challenges in clinical trial design and performance:

- Need for equipoise
- Use of designs specifically for small study populations

- Use of observational/natural history studies where indicated
- Incorporation of data (culled from large-scale, central databases) to augment clinical trial data
- Consideration of published data (if data accuracy and precision can be verified)
- Application of extrapolation when possible
- Dose escalation critical to determining optimal dose, and dose-related improvement in clinical condition
- Randomization with blinding (especially when examining trial data)
- Application of extrapolation (promoted by FDA when possible)
- Dose escalation (critical to determining optimal dose) dose-related improvement in clinical condition
- Randomization with blinding (especially important when reviewing trial data)
- Need for commercially available pediatric formulations
- Development of validated, good clinical practice (GCP)-compliant assays (FDA will require that assays are validated)
- Incorporation of biomarkers and patient-reported (or parent-reported) outcomes to minimize the need for invasive testing (especially important in pediatric studies).

Dr. Zajicek next discussed the need for outcome measures that are clinically relevant and that correlate with the results of invasive testing. She cited muscular dystrophy and inflammatory bowel disease (IBD) as examples of conditions for which the best outcome measures have yet to be determined. She pointed out that FDA has been meeting with advocacy groups to identify the best clinical outcome measure for IBD, but to date, there has been no agreement among these groups, although a mutually agreed-upon outcome measure would help avoid the need for invasive procedures.

Noting that premature neonates are not just small infants, Dr. Zajicek identified the need for research in certain key areas:

- Mechanisms of neonatal conditions related to prematurity
- Feasible outcome measures correlated to long-term neurodevelopmental outcomes.

She noted that sound basic science will lead to a drug target, which in turn, will lead to a drug. She also pointed out the need for a feasible measure that will correlate with a long-term outcome.

Dr. Zajicek concluded her presentation by summarizing key lessons learned since the BPCA program was first established. While much progress has been made, several fundamental challenges remain:

- Need for oversight, defined lines of communication, predetermined reporting structure, and ongoing discussion and collaboration
- Bridge the current disconnect between training and application of knowledge.

She emphasized that knowledge of GCP does not necessarily translate into application, and that it is crucial to embed on-the-job training/apprenticeship/mentorship programs as part of all clinical trials. She also underscored the need for data sharing, pointing out that some trials could

possibly have been avoided if published information had been stored in a central, accessible repository.

Pediatric Drug Development: The Next 10 Years

Lynne Yao, M.D., Associate Director, Pediatric and Maternal Health Staff, Office of New Drugs, Center for Drug Evaluation and Research (CDER), Office of the Commissioner, FDA

Dr. Yao began her presentation by reviewing the Pediatric Drug Development General Principles, as published in the FDA Guidance to Industry (2000):

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

Dr. Yao also explained that the FDA is currently working on GCP-E11. She then presented a timeline that presented a brief history of pediatric drug development, 1977–2014:

- **1977:** The American Academy of Pediatrics (AAP) Committee on Drugs publishes statement calling for drugs to be tested in children if used in children. For the first time, there was direction regarding whether or not it was possible to conduct clinical trials with children, whether it was necessary to do clinical trials with children (rather than merely scaling back dosages based on child age and weight), or whether it was ethical to conduct clinical trials with children.
- **1979:** FDA issues first pediatric labeling requirement.
- **1994:** Final rule, Revisions to Pediatric Labeling issued; extrapolation concept first described, although somewhat vague regarding what information should be added to the label
- **1997:** Food and Drug Administration Modernization Act (FDAMA) enacted, with incentive provisions to industry to conduct clinical trials/studies with children
- **1998:** Pediatric Rule issued: with first requirements for pediatric studies; FDA can require pharmaceutical firms to conduct studies in children
- **2000:** ICH E11 published
- **2002:** BPCA signed into law; Pediatric Rule struck down
- **2003:** Pediatric Research Equality Act (PREA) signed into law
- **2007:** Pediatric Regulation enacted in the European Union (EU); the FDA Amendments Act (FDAAA) reauthorizes BPCA and PREA; Pediatric Review Committee (PeRC) created; Pediatric cluster initiated
- **2012:** Food and Drug Administration Safety and Innovation Act (FDASIA) permanently reauthorizes BPCA and PREA
- **2014:** ICH E11 Addendum EWG established; working on currently with international partners.

Dr. Yao lauded participants for their efforts and commitment to advancing the public health of children worldwide. She next identified several considerations and guiding principles for pediatric product development, including:

- Ethical considerations: Children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provide informed consent personally (i.e., adults). Absent a prospect of direct therapeutic benefit, the risks to which a child would be exposed in a clinical trial must be “low.” Children should not be placed at a disadvantage after being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care.
- Feasibility considerations: The prevalence and/or incidence of a condition are often much lower compared to adult populations.

Dr. Yao summarized the key components of the BPCA and PREA statutes. She then discussed the number of WRs issued during 1998–2015. She explained that the number of WRs is actually less than in previous years, largely because in the early years of the Act, industry sponsors were more willing to conduct trials when incentivized by FDA. Since PREA passage, more sponsors have declined a WR. Dr. Yao did point out that the FDA must review all indications and uses for proposed studies.

She also discussed WRs issued in 2015 by therapeutic area:

- Rheumatology
- Psychiatry
- Nephrology
- Oncology
- Ophthalmology
- GI/Inborn Errors of Metabolism
- Endocrinology/Metabolism
- Dermatology
- Cardiovascular
- Anti-Viral

Of the 10 conditions listed, Dr. Yao noted that the greatest number of WRs issued were within the oncology therapeutic area, most likely because it is extremely difficult to get PREA approval for oncology studies.

Dr. Yao further noted that as of 2016, more than 650 products have been labeled with pediatric-specific information. She also pointed out that this increased experience and understanding has influenced pediatric clinical trial design, pediatric extrapolation, and pediatric formulations. She noted that the number of pediatric labeling changes in 2016 is anticipated to meet or exceed those approved in 2015.

Dr. Yao next discussed pediatric extrapolation, noting that:

- Efficacy may be extrapolated from adequate and well-controlled studies in adults to pediatric patients if:
 - The course of the disease is sufficiently similar
 - The response to therapy is sufficiently similar
- Dosing cannot be fully extrapolated
- Safety cannot be fully extrapolated.

She pointed out the need for verifiable data to support recommended dose-effectiveness and safety. Dr. Yao discussed an Office of Pediatric Therapeutics review, first published in 2011, based on 166 products with submitted pediatric studies between 1998 and 2008. A second review, completed in 2016, was based on 157 products with submitted pediatric studies between 2009 and 2014. The second review reported that partial extrapolation decreased from 68% to 29%.

Dr. Yao explained that these changes in extrapolation likely were due to:

- Evolving science and knowledge from the pediatric trials that allow one to be more confident in assumptions
- Failed pediatric trials and better understanding of the differences between children and adults
- New science in molecular or genetic biology.

Dr. Yao next described the challenges facing the BPCA program in the 21st century:

- Pediatric-specific diseases
 - Neonates and pre-term infants
 - Rare diseases, including pediatric cancers (without specific legislative initiatives to clamor for dealing with these conditions)
- Long-term safety
 - Chronically administered drugs
 - Drugs administered during specific developmental periods (both immediate and long-term)
- Improving efficiency in pediatric product development
 - Coordinated global development programs
 - External and international collaborations
 - Clinical research networks
 - Innovate clinical trial designs
- Expediting product approval for adults (often, current review/approval takes 9-10 years of off-label use)
- Providing incentives/rationale to practitioners to enroll pediatric patient in clinical trial.

Dr. Yao discussed the role of biomarkers, and how to expedite the process of identifying and using biomarkers in product development. She outlined the key components of a strategy to determine what biomarkers will help advance and predict clinical benefit:

- Identify a target population for study
- Population is more likely to respond to treatment based on the disease and the mechanism of action of the drug
- Refine dose and/or dosing interval in Phase 2 trials (using adult data to determine dose in children)
- Changes in pharmacodynamic markers are helpful in determining optimal dose for later phase trials.

Dr. Yao discussed biomarkers as a substitute for clinically meaningful endpoints, as well as surrogate endpoints. She cautioned, however, that not all biomarkers, even clinically useful biomarkers, are suitable as surrogate endpoints. In discussing surrogate endpoints (an endpoint that utilizes a biomarker that is intended to substitute for a clinically meaningful endpoint), Dr. Yao pointed out the necessity of validating a surrogate endpoint, including evidence that the biomarker must:

- Be reproducible within patients
- Be responsive to clinically meaningful changes in disease activity
- Be defined with respect to its temporal relationship with disease activity
- Change in expected direction
- Lie in the causal pathway of the disease.

She also noted that identification of a potential biomarker that could be used as a surrogate marker in Phase 3 trials requires careful and early planning, as well as discussion and concurrence of plans with the review division.

In summary, Dr. Yao reiterated:

- Partial extrapolation may expedite development of pediatric products because an adequate and well-controlled trial may not be required
- Partial extrapolation relies on establishment of similarity of exposure-response between adults and pediatric patients
- Confidence in partial extrapolation relies on selection of a response that is clinically meaningful, with a biomarker that can substitute for a clinically meaningful endpoint.

Dr. Yao next discussed international collaborations, including the Monthly Pediatric Cluster Conference, with representatives from the European Medicines Agency (EMA); Japan Pharmaceuticals and Medical Devices Agency (PMDA); Health Canada (HC); and the Australia Therapeutic Goods Administration (TGA). She also discussed the ICH E11 (pediatrics) addendum, which issues updates on topics that include extrapolation, modeling and simulation, and ethical issues.

Dr. Yao presented an overview of various pediatric research initiatives and networks to advance an infrastructure for clinical studies that are reliable, consistent, and valid. These initiatives include the International Neonatal Consortium (INC) and the Pediatric Trials Consortium (PTC), with a plan to advance to an independent nonprofit (Institute for Advanced Clinical Trials for Children). European Research Network initiatives include the European Network of Pediatric Research at EMA (Enpr-EMA); GriP (Global Research in Paediatrics), Consortium for Innovative Therapies for Children with Cancer (ITCC), Paediatric European Network for Treatment of AIDS (PENTA); and the UK Clinical Research Network (UK CRN).

Dr. Yao next described the need for an improved framework for pediatric extrapolation that includes a review of evidence to support similarity of disease and response to therapy, as well as a review of evidence needed to fill gaps in understanding. She also discussed the application of Bayesian modeling methodology in pediatric trials, as a way to use or borrow information from other pediatric trials, and as a formal approach for incorporating prior information into the planning and analysis of future studies. Dr. Yao briefly described the use of master protocols as a way to increase the efficiency of clinical trials, emphasizing the need for collaboration among academic investigators and/or industry sponsors with input from regulatory authorities.

Dr. Yao discussed the role of “big data” and the need to develop an overall framework to evaluate large, often proprietary, databases. She emphasized the need to recognize and understand the difference between data and evidence, and to differentiate worthwhile and relevant data from “junk” and unverifiable information.

Dr. Yao briefly discussed pregnancy and lactation as a key challenge to be addressed in pediatric drug development, noting that the Pregnancy and Lactation Labeling Rule, published in 2014, does not address methods to improve collection of information on use of drugs during pregnancy and lactation.

Dr. Yao concluded her presentation by emphasizing that children are protected through research, not from it. She also summarized key advances and milestones since enactment of the BCPA:

- BPCA and PREA have led to incorporation of pediatric-specific labeling in more than 650 products
- Government, advocacy groups, and industry are committed to collaboration to increase availability of safe and effective treatments for pediatric patients
- FDA is committed to working with external stakeholders to improve efficiency of pediatric clinical trials
 - Innovative clinical trial designs (efficacy and safety)
 - Improved framework for pediatric extrapolation
 - Clinical trial networks
 - International collaborations
 - Use of big data
- Improved collection of data on use of drugs during pregnancy and lactation

Questions and Answers

Question 1 (Dr. Silverstein): Your presentation cited examples and potential initiatives to bring international groups together. Is FDA leading efforts to develop these international registries? What is the FDA's role in biomarker development?

Response (Dr. Yao): While FDA's role (as well as NICHD's role) is not to actually staff or conduct these studies, it does serve as an "internal champion" to advance these initiatives. Once a study is underway, in addition to its initial role, FDA may become involved; the funding entity may keep the Agency informed as to study progress to assist, but not to lead the study conduct. However, as the study progresses, advocacy groups and the public will look to the FDA and other regulatory agencies for guidance and direction regarding these efforts.

Question 2(a) (Tonse Raju): How does extrapolation work with newborns?

Response (Dr. Yao): While this is an important question, it is also important to look at other age groups as well – school-aged children, and teenagers. How does extrapolation work with any specific age group? Another consideration is perhaps that chronologic age is not necessarily a great biomarker, although it is easy to measure. Perhaps another biomarker such as post-conceptual age is more useful. Extrapolation does not refer specifically to any pediatric age group or population. The determination on whether or not to use extrapolation refers to what the science tells us in regards to a particular drug.

Question 2(b) (Tonse Raju): Please address the importance of developing registries that allow us to follow patients long-term post exposure to a specific drug or treatment.

Response (Dr. Yao): This issue speaks directly to the need for enlisting patient and parent groups, academicians to develop systems (networks, registries, data collection systems, etc.) to be able to collect the data that we think that will help us decide about long-term safety in any given exposure(s).

Dr. Zajicek commented on biomarkers, noting that each subspecialty at NIH considers itself different from all others, but in reality the various NIH Institutes and Centers share the same challenge—how to determine what should be the most relevant or what should define a specific biomarker. She also noted that this is as much an advocacy issue, as it is a clinician, researcher, or regulator issue.

Question 4 (Dr. Benjamin): When considering biomarkers vs. drug development, what convinces us that using a specific biomarker is the way to go? It would be helpful if one could refer to (1) a flow chart that outlines the process relating to biomarker selection or (2) a list of 10 biomarkers that work in a specific condition (based on individual NIH division determination). Would another option be to identify five key studies that one can refer to that will convince the researcher to get a biomarker done and for the researcher to assess whether or not that effort is worth doing for a study of a specific condition?

Response (Dr. Yao): It is important to clarify the biomarker qualification process for a single development program, disease, or drug in children. We don't need to go there; it is a very involved, very intensive process. However, once a biomarker qualifies as an endpoint for specific use, everyone can use it. We agree that it would be very helpful if we could develop a framework on how to evaluate what level of evidence is needed, how much evidence you have to have in this particular disease for this particular population to use this specific biomarker as an endpoint, or to establish dose response to guide decisions about whether there are the resources available to prioritize now.

Question 5 (Dr. Kearns, via Webinar): How might either NICHD or FDA utilize the new resource of the IDeA States Pediatric Trial Network which is part of the new ECHO initiative at NIH?

Response (Dr. Zajicek): When the National Children's Study ended, some funds were transferred to other NICHD programs. One of those was the Environmental Influences on Child Health Outcomes (ECHO) program that followed cohorts of children studying topics, such as neurodevelopment and obesity, among others. In addition, the Institutional Development Award (IDeA) program, coordinates funding to States that typically don't receive NIH monies. These so-named IDeA States usually are rural or less-populated States that do not have clinical trial sites. Through this program, they will have the capability to allow children in IDeA States to be involved in NIH research. This is a great opportunity for academic and IDeA States to become enrolled in NIH research.

Dr. Taylor-Zapata closed the discussion by reading a statement from Dr. Ward:

“Evaluation of long-term outcomes is a very complex process that must control for the original reason for treatment, as well as potential co-treatments, co-morbid conditions, and intervening events in order for it to provide valid data.”

Pediatric Clinical Pharmacology Training: The Next Generation

George Giacoia, M.D., Medical Officer, OPPTB, NICHD, NIH

Dr. Giacoia discussed the evolution of adult and pediatric clinical pharmacology from a historical perspective, focusing on the status and results of the T32 teaching program virtual network. He pointed out that through this program, NIH has provided an infrastructure for studying clinical pharmacology. Dr. Giacoia noted that the research landscape in pediatric clinical pharmacology is dotted with vast areas of lack of, or insufficient, knowledge. Filling those knowledge gaps is fundamental. The T32 program provides a platform for sharing information from investigatory-and academia-based studies while training physicians and pharmacists in pediatric clinical pharmacology and what Dr. Giacoia referred to as a discipline in evolution. He presented a graphic that highlighted key elements and challenges of pediatric therapeutics, including lack of efficacy, patient-oriented therapeutics, “disease”-oriented therapeutics, and drug-oriented therapeutics.

Dr. Giacoia also described the challenges facing the continually evolving training paradigm:

- Need to address knowledge deficits in the role of ontogeny in functionality of receptors, transporters, pathways, and drug-metabolizing enzymes (DMEs) during different developmental stages
- Biomarkers in pediatrics: uses and limitations—it is critical to recognize that biomarkers are not a “magic bullet” that will solve all study challenges
- Developmental toxicology in the “omics” era
- Adult clinical pharmacology at a crossroads: transition into systems pharmacology
- Developmental pharmacodynamics knowledge gap
- Need to provide the scientific basis for extrapolation of adult efficacy studies to pediatrics; the problem of null or failed pediatric drug trials and lack of pharmacodynamics data.

He next described several reasons why almost half of drug trials for labeling failed to demonstrate efficacy:

- Phenotypic expression of pediatric diseases often differs from similar conditions in adults
- Increased recognition of differences in disease/condition pathophysiology between birth and adolescence and adults
- Validity of adult-derived endpoints, outcome measures biomarkers and pharmacodynamic measurements has not been established
- Empirical opinion-based comparisons of natural history of diseases
- Different etiologies
- Differences between adults and children never studied.

Dr. Giacoia explained that the initial NICHD Pediatric Clinical Pharmacology Request for Applications (RFA) arose from the need to train more clinicians and practitioners in pediatric clinical pharmacology. Recipients of the first award were Children’s Mercy Hospitals and Clinics, Kansas City; Cincinnati Children’s Hospital Medical Center; and the Indiana University pharmacology program. The goal of the T32 program was to address two key questions:

- Could T32 NIGMS adult programs in clinical pharmacology provide trainees in pediatric pharmacology the necessary training in “omics” research and technology?
- Could an initial pediatric supplement to NIGMS T32 clinical pharmacology lead to development of faculty in pediatric pharmacology and program at the clinical pharmacology department?

Today, the NICHD and NIGMS-NICHD T32 virtual network consists of 11 institutions, whose members are expected to interact with others linked by a NICHD-created SharePoint Web site. This site, called PedPharmHub, is intended to facilitate discussions among trainees and to develop research protocols across sites. Network members are encouraged to form special interest groups (SIGs), and all T32 trainees are expected to participate in cross-institution interactions. Trainees are required to attend an annual in-person meeting, where they present their ongoing or completed research.

Dr. Giacoia pointed out that participation in the T32 program provides significant added value to trainees, including the opportunity for:

- Participation in a harmonized pediatric clinical pharmacology core curriculum
- Interaction with fellows in other T32 programs
- Access to educational material developed by the NICHD and participating programs
- Exclusive access to the dedicated pediatric clinical pharmacology site PedPharmHub
- Access to experts in other programs for individual queries or as member of a research team
- Participation in SIGs across various sites
- Interaction and collaboration with other pediatric pharmacology fellows in the same pediatric subspecialty
- Possibility of expanding fellow's own research or accessing needed technology or laboratory analysis
- Development of, or participation in, multidisciplinary or cross-discipline projects in response to NIH funding opportunities
- Elective and targeted rotation in other T32 program sites
- Interaction with adult clinical pharmacology fellows in the design of a pediatric-adult pharmacology bridge

Dr. Giacoia emphasized that Pharm.D./Ph.D. fellows can interact and collaborate with other fellows and faculty to respond to NICHD initiatives (e.g., developmental pharmacology, pediatric formulations), and enjoy membership in a unique group of trainees rather than functioning as isolated fellows in an adult medicine environment.

He next described several important issues confronting pediatric clinical pharmacology curriculum development:

- Definition of pediatric clinical pharmacology
- Pediatric pharmacology vs. pediatric therapeutics
- Customized curriculum - different and complementary tracks for M.D.s versus Ph.D.'s and Pharm Ds
- Use of a modular approach with core and advanced content
- Links to other related areas: bioinformatics, systems biology, basic pharmacology.

Dr. Giacoia noted that after considerable discussion and input, program developers adopted the current definition of pediatric clinical pharmacology:

Pediatric clinical pharmacology is a translational discipline that integrates our knowledge of changes in biochemistry, physiology and pharmacologic response during differentiation, growth and development, from conception to adulthood, with the basic tools of human pharmacology and applied pharmacology to optimize pharmacotherapy in the pediatric patient population.

Dr. Giacoia also noted that the course outline incorporates the suggestions of the NICHD Core Curriculum Committee. A total of 31 lectures are divided into 7 modules:

- Pharmacometrics

- Drug metabolism and transport
- Assessment of drug effects
- Pharmacotherapy
- Drug effects and disposition in special settings/pediatric populations
- New technology/pediatric formulations
- Research/publishing/academia.

He explained that trainees are required to attend at least 75% of the weekly lectures. Speaker slides are shared in advance so that trainees can actively participate in the discussions. Training fellows are required to post at least one question or comment on PedPharmHub before each Webinar; questions are read aloud by the Webinar moderator. Dr. Giacoia noted that the program has been expanding to international sites. As of November 2016, attendees from a total of 22 different countries have participated in the program.

Dr. Giacoia also described the Sumner J. Yaffe Memorial Lecture Series, which focuses on topics relevant to pediatric clinical and developmental pharmacology. He explained that a subset of lectures within this series (cross-cutting or “bridge lectures”) examines the differences and similarities in diagnosis, natural history, phenotypic expression, pharmacology, response to treatment, and/or outcomes in adults and children.

Dr. Giacoia presented data on T32 fellows who graduated during 2012–2016. Of the 44 program fellows graduated during that time period, 64% have remained in academia or in academia-affiliated hospitals. Very few graduates are in private practice. Twenty-six first-year or returning fellows represent the following subspecialties:

- Anesthesiology
- Cardiology
- Critical Care
- Developmental & Behavioral Medicine
- Genomics
- Hematology/Oncology
- Neurology
- PB/PK Modeling
- Pharmacology
- Psychiatry
- Pulmonology
- Rheumatology
- Rheumatology/Immunology

Dr. Giacoia mentioned that NICHD has been approached by the National Institute of Mental Health (NIMH) to implement an interagency agreement similar to the one with NIGMS. However, the curriculum would be different, and would involve one or more trainees in one of the five T32 NICHD units, with a major emphasis on how to conduct clinical drug trials in psychiatry.

Dr. Giacoia outlined several programmatic goals for 2016–2017:

- Continue and expand interactions between fellows in T32 NICHD and NIGMS T32 programs in pediatric clinical pharmacology, U54 trainees in developmental pharmacology, and OPRU
- Encourage training of Pharm.D. and Ph.D. fellows in pharmacology with emphasis in pharmacometrics, basic science, and basic-translational pediatric therapeutics research
- Expose pediatric subspecialist fellows to principles of clinical pharmacology
- Increase interaction between pediatric subspecialists and pediatric clinical pharmacology
- An added curriculum objective will be teaching all fellows the limitations of using extrapolation from adult efficacy trials to pediatrics and the significant number of failed pediatric drug trials.

To achieve those goals, Dr. Giacoia described key activities for the upcoming year:

- Actively use PedPharmHub to prepare manuscripts and create research protocols as part of SIG activities
- Continue with general interdisciplinary journal club and journal clubs organized by SIGs
- Develop a basic subspecialty- specific introduction to pediatric clinical pharmacology and therapeutics (fellow-to-fellow exchange).

Dr. Giacoia closed his remarks by stressing the need for continued and expanded interdisciplinary collaboration, emphasizing the need for:

- Teaching of pharmacology and therapeutics at all levels (from medical school to post-doctoral and across disciplines)
- Teaching and development of a new type of translational science pharmacologist well versed on the use of “omics” technology and application of systems biology to pediatric therapeutics and pharmacology
- Formation of teams of researchers rather than single investigator-initiated proposals.

Questions and Answers

Dr. Taylor-Zapata read a question submitted by Dr. Kearns:

Question: Would NICHD consider supporting pediatric pharmacology fellows at institutions or academic pediatric medical centers that have expertise in the discipline and have evolving programs supported by the institution or philanthropic funding?

Response: Dr. Giacoia indicated that NICHD is limited by the type of initiative, but he agreed that there is a need to expand the number of fellows, and finding ways to engage other sources of funding is very welcome.

Pediatric Clinical Trials: From Development to Implementation

Danny Benjamin, M.D., Ph.D., Chairman, PTN; Associate Director, Duke Clinical Research Institute

Dr. Benjamin began with a brief overview of the PTN, noting that the overarching goal of the PTN is to:

Create an infrastructure for investigators to conduct trials that improve pediatric labeling and child health.

Sponsored by the NICHD, since its establishment, the PTN has achieved success in improving dosing, safety information, labeling, and ultimately child health. Dr. Benjamin summarized the process that the PTN follows in selecting potential studies:

- NIH develops a priority list of off-patent therapeutics
- Investigators submit study concept sheet to PTN
- PTN Administrative Core reviews for quality of science and feasibility
- If approved, PTN forms protocol development team of protocol chair, thought leaders, pharmacologists, and operations experts
- NIH provides small amount of funding for protocol development
- PTN sends protocol and budget to NIH
- PTN selects sites from Rapid Start Network (RSN) based on site study interest, availability, and previous history of enrollment
- PTN executes trial.

Dr. Benjamin noted that the overarching intent of the process is to identify gaps in labeling, to determine if a proposed trial is realistic and feasible, and if the proposed clinical trial has potential benefit for children. He reviewed the initial contract 2010 Scope of Work (SOW), and pointed out that the PTN has made significant achievements since then:

Projects

- 45 Task Orders; 32 projects; 21 clinical trials
- Phase I-IV studies; meta-analyses; retrospective analyses; electronic health record (EHR) data

Enrollment

- Over 160 pediatric sites in 5 countries
- 6,000 children enrolled

Across therapeutic areas

- 74 total molecules; 15 active INDs
- Hypertension, Neonatology, Infectious Diseases, Obesity, Neurology, Psychiatry, Critical Care, Gastroenterology, Pulmonary, Hematology, Oncology

Data for 10 molecules have been submitted to FDA, with more than 20 products with planned submission by 2017.

He also noted that studies of 10 molecules and 1 device completed PTN studies. It is not unusual for those studies to involve more than one trial per entity. NICHD-sponsored label changes have been noteworthy, especially for off-patent therapeutics, listed below:

Drugs

- Pralidoxime
- Propylthiouracil
- Nitroprusside
- Meropenem
- Lisinopril
- Lorazepam – Status Epilepticus

Device

- 2D Mercy Tape 510K cleared.

Dr. Benjamin also identified the therapeutics planned for submission by June 2017:

- Caffeine citrate
- Diazepam
- Isotretinoin
- Lorazepam – Sedation
- Methadone
- Ondansetron
- Pantoprazole
- Rifampin
- Trimethoprim-sulfamethoxazo.

While emphasizing the importance of the collaboration of the entire team, Dr. Benjamin reiterated that there are significant challenges inherent to pediatric clinical trials:

- Limited number of patients and low consent rates
- Limited blood volume
- Perceived study risks – blood draws
- Sick population – increases variability
- Variability in site enrollment
- Variability in site outcomes
- Clinician concerns/beliefs about therapies and trials
- Competing research priorities
- Lack of trained pediatric clinical investigators
- Lack of pediatric clinical pharmacology expertise.

Dr. Benjamin pointed out that variability is the “hallmark” of pediatric drug development. He also acknowledged that there are significant challenges, most of which revolve around enrollment, and the limited number of patients eligible for a pediatric clinical trial. He suggested that whenever possible, investigators should consider limiting both inclusion and exclusion criteria when developing their study concept. Dr. Benjamin briefly listed typical inclusion/exclusion criteria for a pediatric clinical trial, explaining that it is typical to see trials with 3 to 10 inclusion criteria, and that it is not unusual to see as many as 20 to 30 exclusion criteria. He cited an example from the Meropenem Trial. The initial study concept, based on 600

infants with surgical necrotizing enterocolitis (NEC), estimated the need for 50 sites during a 10-year period. In actuality, 200 infants were studied at 25 sites, over 18 months. Study investigators negotiated a trial re-design and sample size that was acceptable to FDA, resulting in an FDA label change for meropenem.

Dr. Benjamin discussed the challenge of limited blood volume, suggesting sensitive drug assays as a solution. He further suggested that minimal sampling methods may pose a possible solution to the need for multiple blood draws, which presents a major issue for parents, as well as an ethical issue for researchers.

Dr. Benjamin also described several site characteristics that could affect enrollment:

- Level of involvement of Principal Investigator (PI)/study coordinator
- Relationship with sponsor and/or coordinating center
- Time to activation (IRB, contracting)
- 24/7 coverage
- Buy-in from clinicians, nurses
- Competing studies.

To meet these challenges, Dr. Benjamin noted that the PTN has been increasing the number of study sites, both within the U.S. and abroad. Currently, the PTN encompasses sites in the U.S., Canada, Israel and Singapore, including academic-and community-based sites. He also discussed the RSN, and the need to cover diverse therapeutic areas, enrolling patients ranging from preterm infants to adolescents. It is also extremely important to identify and adjust for differences in site characteristics, and elicit site input in protocol design and feasibility, site materials, and enrollment troubleshooting.

Dr. Benjamin explained that it typically takes between 5 to 12 months to get academic center contracts in place. He described the Duke Clinical Research Institute (DCRI) RSN master service agreement.

Dr. Benjamin identified extrapolation and the use of master protocols as major issues critical to pediatric drug development during the next 10 years. He briefly described the use of safety master protocols in the SCAMP Phase 2/3 trial (randomized, multicenter, open-label Safety study of Clindamycin, Ampicillin, Metronidazole, and Piperacillin-tazobactam in infants with complicated intra-abdominal infections).

Dr. Benjamin next discussed the issue of clinician beliefs/concerns about adapting the master protocol model. He described a study of the use of furosemide. He pointed out that some clinicians voiced concerns that the drug was not labeled for infants, and that there was little evidence of efficacy or safety. Also, many sites claimed that this therapeutic is never/rarely used, and if used, doses are never greater than 1 mg/kg. It is not ethical to randomize babies because (1) we use this therapeutic all the time and we know that it works; (2) because it doesn't work and no one ever uses it; or (3) we know what we are doing with the drug. Dr. Benjamin noted that existing data from EHRs and a retrospective chart review were used to inform clinicians,

pointing out that furosemide was the fifth-most-common drug used in neonatal intensive care units (NICUs) for babies less than 1,000 grams birthweight in the U.S.

He also addressed the challenge of competing research priorities, focusing on the NICHD Neonatal Research Network. More research is being conducted to meet regulatory requirements, creating what constitutes a waiting list. However, resources are limited. Dr. Benjamin pointed out that a PTN goal is to complement and fill the gaps of other networks. He strongly advocated allowing for co-enrollment in PTN studies, and recommended discussion of co-enrollment with potential site investigators during the site selection process.

Dr. Benjamin also identified the lack of trained investigators and the lack of pediatric clinical pharmacology expertise as significant challenges. He next shared several lessons learned:

- Be collaborative and have frequent discussions with Network partners, including NICHD, the EMMES DCC, and FDA, and with sites and investigators (consider pre-IND meetings)
- Maximize protocol efficiency, by incorporating
 - Simple design
 - Inclusive inclusion criteria
 - Multiple drugs in same protocol
 - Standard of care procedures
 - Pre-trial modeling and simulation
 - Efficient data analysis method
- Maximize operational efficiency, by incorporating
 - Central IRBs
 - Master Contracts – RSN
 - Careful site selection – site metrics
 - Single point of contact per support department
 - Template documents when appropriate.

Dr. Benjamin concluded his presentation by stressing the need for continued and expanded collaboration and partnering among studies, including advocating for co-enrollment, whenever feasible.

Question (Dr. Giacoia): Describe quality control over the international sites.

Response (Dr. Benjamin): It has been relatively easy for the Canadian studies, and PTN experience with quality of data from sites outside North America has been positive so far. Also, the PTN does not do an IND trial first; an opportunistic PK study was conducted to assess data quality. To date, the quality of data compiled from other international sites—Israel, Singapore, and EU—has been excellent.

Lessons Learned—The DCC Perspective

Ravinder Anand, Ph.D., BPCA DCC PI, Vice President/Senior Statistician, the Emmes Corporation

Dr. Anand noted that most of the issues and challenges that he will discuss have been identified in earlier presentations. He began by briefly describing Emmes roles and responsibilities since the BPCA Data Coordinating Center (DCC) award in 2009. Key elements of the project include:

- Study design and management
- Data collection and quality assurance
- Statistical design and analysis
- Regulatory guidance and submission support
- Medical monitoring and pharmacovigilance
- Data Monitoring Committee (DMC) support
- Clinical site monitoring and auditing

Dr. Anand next discussed several key lessons learned regarding study design. First and arguably most important, he emphasized that it is critical to get FDA input on study design, endpoints, and analysis plans to ensure data generated by the study will be adequate to address labeling gaps, while ensuring long-term safety of the medications being studied. He also noted that NIH resources are limited.

Dr. Anand also identified several key challenges to ensuring sound statistical study design:

- Small patient population
 - Large phase 3 efficacy trials are not always feasible
 - A large number of sites (usually more than 50) are needed to enroll a moderate number of participants (average site may enroll only 5 participants) contributing to variability in treatment effect estimates
 - Adaptive designs with response adaptive randomization may be useful in limited settings
 - Observational studies will be needed to obtain additional safety data required for FDA labeling; however, determining the relationship to drug and dose response is difficult in observational studies
- It may be necessary to modify enrollment criteria to allow for Standard of Care (SOC) dosing

He next pointed out several ethical issues relevant to the statistical design of pediatric studies:

- Placebo-controlled trials often are not an option
- Sites may not be willing to enroll participants in a randomized trial due to lack of equipoise
- Use of historical controls is another option, but it is important to understand the limitations of historical controls, and equally important, the need to match studies with similar design (procedures/duration) and patient populations.

Dr. Anand described several other key challenges:

- SOC treatments often are not labeled for indications under study
- Observational studies for evaluation of safety have significant limitations
 - Any potential source of bias should be identified during study design and adjusted for using advanced statistical models whenever possible
 - Consider using a propensity score approach to adjust for baseline differences in treatment groups.

Dr. Anand discussed issues relevant to safety reporting and monitoring, in particular, the need to train sites regarding safety data reporting. This may involve layering clinical trial reporting on the standard of care, while recognizing that most EHRs are not designed for research purposes. He also pointed out the need to conduct limited training by Webinar, given that in-person training usually is not feasible. Dr. Anand further explained that there are numerous challenges to conducting studies with hospitalized Intensive Care Unit (ICU) subjects, including identifying AEs and serious adverse events (SAEs), noting that all subjects enter the study as an SAE, and that there is considerable variability in AE reporting across sites.

Dr. Anand discussed other issues, including:

- Outcomes of special interest (OSI), noting OSIs allow for collection of key safety data in a consistent, standardized manner. Collection of OSIs that are relevant across neonatal trials can be augmented with specific OSIs for a given trial based on FDA input.
- Monitoring safety, including standardizing data collection at sites, with DMC oversight.

Dr. Anand went on to discuss data quality, noting that:

- BPCA studies include sites/PIs that may be inexperienced in conducting clinical trials designed for label changes and monitored by FDA; these sites require significant ongoing training/support to ensure highest quality data and study conduct
- Data extraction and monitoring from EHRs is not always optimal
- Mechanisms to improve study conduct and data quality include:
 - Continuous investigator meetings/trainings/engagement
 - Personalized site activation and regulatory support
 - Data walk through following first enrollment
 - Extensive use of study website
 - Training/education during monitoring visits and all-site calls
 - Flexible study designs to minimize dosing errors, sample collections, especially for in-hospital studies.

Dr. Anand next discussed issues related to site preparation for FDA audits, explaining that the FDA will audit sites/labs as part of the Agency's review process for labeling changes to assess the level of confidence in study conduct and data under review. These audits present a number of challenges, as well as lessons learned:

Challenges

- Limited resources
- Long gaps between first patient enrollment and final FDA audit will likely result in loss of key study staff
- FDA record storage requirements for 2 years post marketing approval is inconsistently interpreted.

Lesson Learned

- Assist site staff with final archival of study files
- Improve site data retention to support FDA audits
- Provide site with electronic Trial Master File (eTMF), including site case report forms (eCRFs), SAE narratives, and deviation summaries
- Create the eTMF structure at the beginning of the trial
- Understand that newer electronic solutions are important yet expensive to implement
- Close out study sites while staff/information (including anecdotal feedback) is still fresh
- Site resources during an audit are likely to be very limited
- Sponsor support is required.

In closing his presentation, Dr. Anand reiterated the need for (and value of) FDA collaborations, noting that pre-submission meetings are critical to present study results and proposed label changes before submission of the final study report and datasets. These meetings also allow for preliminary feedback and provide an opportunity to conduct additional analyses to support study conclusions, thereby expediting the label change process.

NIH Clinical Trials Reforms: Improving Stewardship and Transparency

Caroline Signore, M.D., M.P.H., Deputy Director, Division of Extramural Research, NICHD, NIH

Dr. Signore explained that her presentation would focus on acquainting participants with the upcoming NIH-wide clinical trials reforms. She noted that these policy changes were rooted in the concerns of many stakeholders about clinical trials supported by NIH. Dr. Signore further explained that the NCI requested that the Institute of Medicine (IOM) review the NCI clinical trials system. In its 2010 review report, the IOM noted that the NCI clinical trials program was “falling short of its potential to conduct the timely, large-scale, innovative clinical trials needed to improve patient care.” Clinical trials seemed to get bogged down, leading to questions regarding the length of time and progress of NIH-supported clinical studies. They concluded that changes were “urgently needed.”

In response to a GAO March 2016 Report to Congress that found that “additional data would enhance the stewardship of clinical trials NIH-wide,” an Institute-wide WG was formed to address the following main concerns about how NIH is monitoring clinical trials and shepherding them to conclusion:

- Large investment, \$3 billion/year
- Variable quality of trial design

- Incomplete registration and reporting of trial results (even despite statutory requirements)
- Inconsistent oversight and monitoring
- Inability to assess across IC's

Dr. Signore referred participants to an October 2016 article in the *Journal of the American Medical Association (JAMA)* that discussed changes in NIH clinical trial policies and the rationale behind those changes. She next briefly described the timeline for these reforms in juxtaposition with the traditional clinical trial lifecycle:

Clinical Trials Process Stage	Reform/Policy Requirement
Initial concept	Good Clinical Practice (GCP) training
Application: clinical trial RFA/FOA	
Application review	
Funding	
IRB review	Single IRB policy
FDA review	Protocol template
Enrollment and data collection	ClinicalTrials.gov registration
Results	ClinicalTrials.gov results submission

Dr. Signore next reiterated the overarching goals of these policy reforms:

- Enhance application and award process
- Increase NIH's ability to assess the merits and feasibility of clinical trial applications
- Improve oversight and transparency
- Increase sharing of results
- Ensure rigor and efficiency
- Improve stewardship
- Maintain public trust respecting the significant investment of taxpayer funds.

She presented the revised NIH Clinical Trial Definition (NOT-OD-15-015, January 25, 2015):

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Dr. Signore also discussed several other policy changes, including:

- **GCP training for NIH awardees involved in NIH-funded clinical trials**
 - NOT-OD-16-148, September 16, 2016; effective January 1, 2017
 - Complement to other required training on human subjects protections
 - Required of all NIH-funded investigators and clinical trial site staff responsible for the conduct, management, and oversight of NIH-funded clinical trials
 - Acceptable courses include those offered by the National Institute of Allergy and Infectious Diseases (NIAID), the National Drug Abuse Treatment Clinical Trials Network, and the Collaborative Institutional Training Initiative (CITI) Program.
- **Policy on Funding Opportunity Announcements (FOAs) for clinical trials**
 - NOT-OD-16-147, Issued September 16, 2016; target effective date: September 27, 2017

- Applications will require specific information about protocols, specific review criteria, and include terms and conditions in Notices of Grant Awards
- Mechanisms will differ by Institute or Center
- Responding to a specific clinical trial FOA is the *only* way to propose an investigator-initiated clinical trial
- Specific review criteria will focus on feasibility and rigor of study design.
- **Use of a single IRB for multi-site research**
 - NOT-OD-16-094, Issued June 21, 2016; effective for applications received on or after May 25, 2017 (n.b.: Since the date of this presentation, the effective date for this policy has been extended to September 25, 2017; NOT-OD-17-027)
 - Applies to all domestic sites in multi-site clinical research, not just clinical trials
 - Improve efficiency
 - Minimize duplicative (often unhelpful) reviews
 - Direct and indirect cost scenarios.

Dr. Signore next discussed the National Center for Advancing Translational Sciences (NCATS) Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB Reliance Platform. She explained that the SMART IRB Reliance Platform was designed as a template/road map to assist applicants by providing flexible resources that investigators nationwide can use to harmonize and streamline IRB review for their own multisite studies.

She presented an overview of the NIH and FDA Request for Public Comment on Draft Clinical Trial Protocol Template for Phase 2 and 3 IND/IDE Studies. Dr. Signore explained that the template was developed in 2016 by FDA and NIH and that it aligns with GCP. A review of comments is currently underway, and there is a possibility of developing an online tool to facilitate template use. There also is a plan to adapt the template for Phase 1 trials, as well as social/behavioral intervention trials. A second draft is expected in the near future.

Dr. Signore noted that the NIH Office of Science Policy (OSP) is the “go to” resource and information repository on all of the upcoming policy changes. She also directed participants to another article, “Sharing and Reporting the Results of Clinical Trials,” which discusses the rationale behind the proposed changes. She discussed the Notice of Proposed Rule Making, which was issued to implement 2007 FDAAA reporting requirements, noting that HHS exercised the option to expand the scope to unapproved products.

Dr. Signore next discussed the Registration and Results Submission on ClinicalTrials.gov—Final Rule. She noted that the Final Rule, issued in September 2016 and effective January 18, 2017 (compliance date: April 18, 2017), outlines requirements for registration and results reporting for studies that fall under the actual rule, specifically, Phase 2 and 3 clinical trials of FDA-approved products.

Dr. Signore then discussed the NIH policy on the dissemination of NIH-funded clinical trial information. She emphasized the importance of distinguishing between the Final Rule and policy, noting that the *policy* applies to *all* NIH-funded clinical trials (not just FDA-regulated trials) regardless of study phase, type of intervention, or whether the trials are subject to the regulation.

Dr. Signore referred participants to an article in the *New England Journal of Medicine* (NEJM), “Trial Reporting in ClinicalTrials.gov — the Final Rule,” which describes how the rule clarifies/expands the statute. The article cautions that for trials subject to the regulation or NIH policy, “...the days of deciding whether or not summary results are worth reporting are over.”

Dr. Signore pointed out that with enhanced reporting in ClinicalTrials.gov, benefits may include minimizing/eliminating conduct of duplicate trials, and most importantly, eliminating trials that are not feasible or that are not safe. She also cautioned that the penalties for noncompliance will be significant—an up to \$10,000/day fine or possible withholding of future funding for the grant and any future grants to the grantee institution. She pointed out that the intent is to underscore that clinical trial results are to be taken seriously, with the goals of enhancing transparency, stewardship, and ethics.

Dr. Signore concluded her presentation by noting that significant activity is already underway throughout NIH, including:

- Draft and release of FOAs, specific elements
- GCP training for NIH staff as well
- Continuing development of protocol template
- Establishing monitoring systems
- Conducting staff and community training
- Enhancing communications
- Developing evaluation plans to assess policy change outcomes

Questions, Answers, and Comments

Question (Ms. Simone): I go to many sites to visit for monitoring, and I agree with a point made earlier that there’s a difference between being trained in GCP and understanding the applicability of it. A lot of institutes have a one-time requirement for training with no refresher classes required. My recommendation is to mandate regular refresher trainings, as the information doesn’t always translate smoothly from when you initially take the training until you have to apply it 10 years later.

Response (Dr. Signore): A refresher course every 3 years is a requirement of this new policy. The quality of training, however, has not been specifically prescribed.

Question (Dr. Benjamin): When it was first launched, the quality of the data posted on ClinicalTrials.gov was often incomplete and questionable. Have you considered putting some of the reporting burden on the PI?

Response (Dr. Signore): The Final Rule requires sponsors or sponsor-designated PIs (i.e., “responsible parties”) to ensure that data are entered into ClinicalTrials.gov. In terms of policy and implementing the policy, ClinicalTrials.gov accepts some of the responsibility for the quality of the data posted; NLM is committed to revamping and

augmenting the site so that it can more readily and more easily take in and present these data, including a standardized format. Dr. Signore noted, however, that these are summary-level data, for example, participant flow diagram, baseline demographics, primary and pre-approved secondary outcome data, with statistical analysis, as well as a copy of the protocol. It is unclear how enforcement will be implemented, including withholding grant funds. There is also the issue of patient-level data. While not part of the current policy or regulation, NICHD is very interested. Participants are encouraged to learn about the Data and Specimen Hub (DASH), the NICHD-sponsored repository. Although submissions to DASH currently are not required, they are strongly encouraged.

Response (Dr. Yao): FDA has recently received updates on this topic; especially the issue of ensuring that results get reported. This has led to discussion on how to determine how to verify the study results. NIH is expending funds and resources on defining the evaluation process and the role that FDA could play in verifying study results. There is concern on the part of FDA about the quality of those results.

Response (Dr. Signore): Typically NLM conducts a quality check of data being entered into ClinicalTrials.gov. She did not have details on the steps taken to assure data quality, but this tends to be a lengthy process with ongoing conversation between NLM and study investigators. The new rule and regulation requires ClinicalTrials.gov to post data within 30 days of submission. NLM has cautioned that it is likely that it will be unable to complete its quality check within that timeframe. Because it is required to comply, NLM is forced to attach a disclaimer to that data. Dr. Signore suggested that investigators should be even surer that they are satisfied that they are submitting high-quality data.

Additional Questions, Answers, and Comments

Question 1: On the map that you showed depicting PTN sites, there appeared to be a paucity of rural sites included in the PTN. How is the PTN going to address that gap?

Response (Dr. Benjamin): The PTN has had significant success in studying molecules where there are hospitals that admit children (not children's hospitals). Most of the PTN work has been done in hospital-based trials that won't have touched those children. It is exciting that certain studies, for example, the antipsychotic protocol are linking up with the IDeA States network. Also, there are sites in the PTN that are not currently enrolling children; these sites do not appear on the map.

Question 2: Can you give reasons why the FDA may reject study data?

Response (Dr. Yao): The main reason for rejection of data has to do with concerns about the reliability and validity of those data. That is, did something happen during the course of the clinical trial that leads us to be concerned about that reliability and validity?

This begs the larger question: Why are we not accepting the results of a study as confirmation of evidence of effectiveness and safety? We are getting better at discussing earlier in pre-submission and pre-IND meetings with sponsors about whether or not the

population, doses, endpoints, and design of the trial will answer the question: Does the drug work for this population for this condition? FDA is trying to help investigators answer the question in the most efficient way.

Question 3 (Dr. Yao) to Dr. Zajicek and NICHD program staff: In this program, how do you deal with the very confident, but wrong, subject matter experts (SME), who refuse to follow the rules?

Response (Dr. Zajicek): One advantage to doing studies by contract rather than by grant is the Contractor Performance Assessment Reporting System (CPARS), where the Government can post specific information about the successes or failures of a study. The CPARS process is painstaking, but worthwhile, and all posted information is publically available.

Response (Dr. Benjamin): There are two scenarios: (1) An investigator who is enrolling and is not behaving in accordance with GCP protocol. In that situation, the PTN has initiated intense monitoring, site visits, conference calls. But also, in the multisite scenario, it is likely that some study investigators may “go off the grid.” In that situation, it is important that the team reacts rationally and prioritize methodically, while salvaging the study. (2) In another scenario, for example, during an FDA meeting, an SME is hired by a pharmaceutical company to advocate for a specific off-patent drug. In this situation, the motivation is to get a metric that can be added to the label that can be used to treat children, whether or not it is in the best interest. The challenge is how to make sure that at the end of this conversation there is clarity regarding a feasible trial that will affect the label, for better or worse. Because the dynamic has changed so significantly, there is much less “great certainty” often expressed at meetings when a pharmaceutical partner is present.

Response (Dr. Zajicek): When the FDA and PTN groups meet, typically an outside PI is present. There have not been any issues with those PIs; everyone has worked well together, which has not always been the case.

Response (Dr. Siegel): PTN is a contract mechanism, with a lot more intense monitoring. Issues are more easily “nipped in the bud.” The contract mechanism allows for the receipt of expected deliverables and close monitoring of study progress.

Question 4 (Dr. Sullivan): What can be done to educate the public to a greater extent regarding research? It seems like we are losing ground with recruitment.

Response (Dr. Benjamin): One potential source of the problem can be with the investigator. Our culture can also be a part of the problem; if the culture is that we need to partner with you to learn more to improve public health, there is greater sustained enrollment. That is why pediatric oncologists have had so much success over the years. When there is an investigator, institution, and family partnership, we see higher consent rates between 8 to 60 % variability by site. Educating families is in our best interest to publicize the data; to not publish is unethical.

Comment: Dr. Yao agreed with Dr. Benjamin regarding a sea change in culture. She suggested that one way to change the culture is to make it a priority for people in a way that makes a meaningful difference for them. She also argued for collaboration with practicing physicians can help in collecting data as part of maintenance and certification.

Question 5 (Dr. Wesley): What is your opinion about a master pregnancy registry?

Response (Dr. Benjamin): He enthusiastically endorsed the idea of a master pregnancy registry. He is currently working with a pharmaceutical company to help develop a registry that they will pilot-test. Dr. Benjamin also noted that he supports the concept of an opportunistic-type registry; however, he cautioned that these registries must allow for a broad-enough inclusion to get information while narrow enough to allow for focused questions that can be addressed and answered from such a registry.

Comment: Dr. Signore announced the launch of beta testing of the NICHD-sponsored PregSource registry. She explained that this registry is designed for pregnant women to register and respond to questionnaires during their pregnancy and in the 3-year post-natal period. Developed as a Web-based platform, the registry will also be developed as a mobile app. She also noted that the hope is that thousands of people will register, as an opportunity to compile information on normal, as well as problematic, pregnancies. The intent is to launch PregSource to the public early next year.

Additional Comments: Dr. Siegel noted that there has been considerable hesitation among families of special needs children to enroll in registries. Also, he noted that researchers are being encouraged to gather opportunistic PK data on women.

Dr. Anand remarked that it has been difficult to follow children for long periods of time to get long-term outcomes; it is expensive and a lot of patients are lost to the study, resulting in questionable data.

He also referred to an article in *NEJM* regarding using registries to do clinical trials. Several benefits and advantages of this approach include that there is a study population in place to draw from; historical data have been collected; and the infrastructure is already in place.

Dr. Giacoia asked about the educational components of PregSource.

Dr. Signore explained that there are other components to PregSource. There are more than 20 partners working with PregSource that have contributed content to the questionnaires, as well as already-developed patient-outreach materials regarding pregnancy. The intent is that women will rely on PregSource as a “one-stop shop” model for reliable and relevant information regarding pregnancy. Based on a woman’s response to the PregSource questionnaires, NICHD can push directly related content back to the woman. These questionnaire data will be de-identified and made available to researchers. PregSource could also suggest other sources of information, including relevant clinical studies. Also, PregSource could be used by trials taking place in other locations on other topics as a tool to enhance follow up.

Ms. Simone noted regarding ClinicalTrials.gov, that perhaps a possible way to lend more credibility to what is reported is to have the monitoring group (if monitoring was conducted) provide statistics.

Dr. Henderson (NIH Intramural Program, Nursing Institute Fellow) noted that the Nursing Institute is now required to submit audits to be uploaded to the IRB. She remarked that there was initial trepidation, but once you undergo the process, there are significant benefits.

Concluding Remarks

Dr. Taylor-Zapata reported on the priority list timeline and finalization process. She explained that input was solicited and received. An internal review was conducted by NICHD. An outside stakeholder has reviewed those nominations. They are now being reviewed by the FDA pediatric division. Once final, the nominations will be published for 2017.

Suzie McCune submitted an announcement to share with participants. A Foundation for NIH- and FDA-sponsored workshop was held recently to develop the framework for criteria development for biomarker qualification. That information has been posted to the Foundation for NIH Website. The link will be provided to participants.

Dr. Taylor-Zapata urged participants to complete and submit the evaluation form. She also urged them to access the newly redesigned BPCA Web site.

Future Directions and Wrap Up

Anne Zajicek, Pharm. D., M.D., Branch Chief, OPPTB, NICHD, NIH

Dr. Zajicek emphasized that the Branch truly appreciates the full partnership between NIH and FDA. She concluded the meeting by presenting a list of “food for thought” topics that she urged participants to consider:

- Science
- Clinical Trial Designs
 - Default enrollment
 - PK/PD Modeling
 - Incorporation of other data
 - Natural history/observational data
 - Data base data
 - EHR
- Outcome Measures
- Patient/Parent/Pediatric Reported Outcomes
- Infrastructure
- Training
- Devices