

**The Network of Pediatric Pharmacology Research Units (PPRU):
History of Accomplishments and Future Role of the Network in
Meeting Needs in Pediatric Clinical Pharmacology**

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Table of Contents

Executive Summary	3 - 5
Section I: The History and Accomplishments of the PPRU	
I. Definition of the Original Problem	6 - 8
II. Structure and Mission of the PPRU Network	8 - 11
III. Key Events in the History of the PPRU	11 - 15
IV. Implications for the Future	15 - 16
V. Specific Aims of the Original PPRU RFA (1994-1998)	16 - 20
VI. Specific Aims of the Second RFA (1999-2003)	20 - 24
VII. Responsiveness of the PPRU in Meeting Changing Opportunities	25 - 32
Section II: Future Challenges	32 - 34
Section III: Proposed Objectives to Meet Current and Anticipated Needs in Pediatric Therapeutics – Future Role of the PPRU	
I. Mission Statement and Objectives for the PPRU	34 - 35
II. Justification for the Proposed Objectives	35 - 41
III. Research Plans	41 - 43
IV. Operational Challenges for the Network	43 - 47
V. Proposed Organizational Structure and Functions	47 - 51
Appendix A: Current Organizational Structure of the PPRU	52
Appendix B: PPRU Publications	53 - 121
Appendix C: Strategic Plan for Neonatal Working Group	122

Executive Summary

The Pediatric Pharmacology Research Unit (PPRU) Network was born out of the recognition that an infrastructure to support pediatric drug development did not exist within academia, the pharmaceutical industry, or the FDA. The PPRU has contributed to the labeling of drugs for children, has generated new information regarding pediatric pharmacology, has provided consultation to the industry and FDA who have struggled to meet the demands of FDAMA and the Pediatric Rule, has been an advocate for children in public policy related to pediatric therapeutics, and is engaged in the training of the next generation of experts to carry on this important work.

During the first five years, the over-riding goal of the PPRU network was to create a platform to conduct pediatric studies that would support pediatric labeling. As the second five-year period began, the commitment of the National Institute of Child Health and Human Development (NICHD) to the PPRU was both continued and enhanced. The RFA for the second five years of the PPRU again recognized the need for clinical studies to support pediatric labeling and drug use information in children. It also acknowledged the continued need for a greater infrastructure for pediatric clinical research. However, the mandate for the network was substantially broadened with a greater emphasis on innovative translational research relevant to pediatric pharmacology.

The network has identified the most critical anticipated research needs in pediatric therapeutics for the next 5-10 years. The research objectives designed to address these needs have been carefully crafted to focus the efforts of the network on areas that:

- are unlikely to be addressed in another way;
- require a high degree of pharmacological expertise resident within the group;
- would be difficult or impossible to conduct at a single site;

- emphasize collaboration with other research groups or organizations in the development of a rational plan for drug assessments in children;
- require unique approaches to meet practical or ethical challenges; and
- have the greatest potential impact on understanding and improving child health.

Over the first nine years, the PPRU has evolved and continues to evolve and mature.

While significant progress has been made in a number of areas, many challenges remain.

Therapeutic areas that have not received adequate attention include disordered sleep, hyperlipidemia, contrast imaging agents, and many psychiatric disorders. Furthermore, alterations in drug distribution, metabolism, disposition, and elimination that are unique to pediatric subpopulations (e.g. neonates) remain to be determined for many important therapeutic agents. Comparative trials, to determine optimal therapy when more than one agent is available to treat a disorder, are fertile ground for further investigation. Drug-disease interactions and the effect of therapeutics in children with multiple diseases have been studied extensively for selected conditions (e.g. cystic fibrosis) but not others (e.g. diabetes mellitus, nephrotic syndrome). Differences in responsiveness (e.g. pharmacodynamics) need to be elucidated for many conditions in children (e.g. hypertension). Drug formulations appropriate for children who are unable to swallow capsules and tablets remain a critical issue for pediatrics. New agents developed from basic research in proteomics and immunology will need to be evaluated in children. Finally, it is conceivable that the risks of biological and chemical warfare may impact the future of the PPRU. To accomplish these goals, new study designs and methodologies will need to be adapted from adult trials or created de novo. It is clear that meeting the changing needs of pediatric patients is an ongoing challenge, one that will require maintenance of the infrastructure necessary to meet new therapeutic needs and opportunities.

The overriding mission of the PPRU is to develop and disseminate new information that facilitates drug development and improves drug therapy for children. The PPRU will actively pursue this mission by focusing on five major goals:

1. Multicenter clinical trials leading to pediatric labeling for drugs, biologicals, and medical devices;
2. Collaborative clinical research that improves pediatric therapeutics but may not lead to pediatric labeling;
3. Translational research that leads to a better understanding of any aspect of drug delivery, disposition, effectiveness, and safety in children;
4. Novel clinical research methodologies in pediatric clinical pharmacology;
5. Training in pediatric clinical pharmacology for health care professionals.

In order to meet the goals set forth above, sites selected for inclusion in the PPRU network will be expected to participate in collaborative research within the network. PPRU sites will also be expected to demonstrate unique strengths that contribute to the overall effectiveness of the network in one or more of the areas outlined under these Research Objectives. Furthermore, it is expected that these areas of concentration or strength at individual sites will be accessible to all sites for network approved collaborative research projects or educational programs. It is not expected that each site will necessarily excel at all five objectives. The strength of the network lies in its diversity and in the willingness and ability of the individual sites to take advantage of the strengths available at other sites. Demonstration of meaningful participation in multicenter collaborative research projects is critical to the success of the network.

To meet the challenges of the future, the PPRU Network will need to evolve. The organizational structure and functions of the network will need to be continually adapted to meet changing opportunities and needs.

Section I: The History and Accomplishments of the PPRU

I. Definition of the original problem – A solution to the therapeutic orphan

The Pediatric Pharmacology Research Unit network was born out of the recognition that an infrastructure to support pediatric drug development did not exist within academia, the pharmaceutical industry, or the FDA. Whereas an extensive infrastructure to support clinical trials of new drugs in adults developed during the three decades following implementation of the Drug Industry Act of 1962, a comparable infrastructure of funding, investigators, clinical research facilities, and expertise in the FDA and pharmaceutical industry to support research in infants and children never emerged. Consequently, approximately 80% of prescription drugs marketed in the United States to the present time were approved and marketed for adult use, but were not adequately studied in infants and children or approved by the Food and Drug Administration for use by children.

The PPRU was the culmination of a long-standing dream and ongoing commitment to change this untenable situation and the product of visionary leadership at NICHD. During the past 30 years numerous individuals and organizations within the pediatric medical community, working with the FDA, NIH and pharmaceutical industry, have sought ways to increase pediatric drug research and, consequently, labeling for children. These efforts culminated in a 1990 workshop on *Drug Development and Pediatric Populations* jointly sponsored by the Institute of Medicine of the National Academy of Sciences, the NICHD, and the American Academy of Pediatrics (AAP). The purpose of this workshop was to identify and make recommendations regarding impediments to drug development for the pediatric population. In retrospect, this was a watershed meeting. Recommendations from the workshop included: 1) that the FDA explore ways to facilitate the approval of drugs for children and inclusion of pediatric information in drug labeling; 2) that economic disincentives to drug development for children be addressed by

granting extended exclusivity to sponsors for drugs that are studied in children and for which data are submitted to the FDA in support of pediatric labeling; 3) that the pharmaceutical industry take a more proactive stance with respect to drug development for children, and 4) that the National Institutes of Health establish a network of pediatric centers to begin to provide the infrastructure that was missing. During the past decade, each of these recommendations has been implemented. Through the committed and visionary leadership of Dr. Dwayne Alexander, Director of NICHD, and Dr. Sumner Yaffe, Director of the Center for Research for Mothers and Children, the PPRU was transformed from concept to reality shortly after the IOM workshop. In 1993 an RFA was issued and in January of 1994, the NICHD funded the first group of pediatric centers to inaugurate the Pediatric Pharmacology Research Unit (PPRU) network.

The PPRU network was a bold experiment by NICHD. Although other networks preceded it, the PPRU was, and continues to be unique in a very significant way. It was the first network intentionally designed to bring together the collaborative efforts of academic investigators, pharmaceutical sponsors, and the NIH to accomplish something that heretofore had not existed. It created a critical mass of patients, research facilities, and expertise in pediatrics and clinical pharmacology under the NICHD umbrella to work in concert with the pharmaceutical industry to conduct pediatric pharmacology research. This was made possible, in large part, by implementation of the U-01 cooperative agreement funding mechanism.

The experiment has been extraordinarily successful, as documented elsewhere in this report. The impact on therapeutics for children is tangible and measurable. The PPRU has contributed to the labeling of drugs for children, has generated new information regarding pediatric pharmacology, has provided consultation to the industry and FDA who have struggled to meet the demands of FDAMA and the Pediatric Rule, has been an advocate for children in public policy related to pediatric therapeutics, and is engaged in the training of the next generation of experts to carry on this important work. With relatively modest funding compared to other networks, the NIH has realized extraordinary results in a relatively short time through

the PPRU network. This is due to the leverage achieved through the addition of industry funding and supplemental support from the PPRU institutions on top of the infrastructure support provided by the PPRU grants.

II. Structure and Mission of the PPRU Network

A. First Five Years: 1994-98

During the first five years, the over-riding goal of the PPRU network was to create a platform to conduct pediatric studies that would support pediatric labeling. The RFA stated, "The ultimate goal of studies conducted by the network is to provide the clinical data on drugs necessary for U.S. Food and Drug Administration (FDA) approval for use in children". The specific aims were: "1) conduct of collaborative clinical trials; 2) conduct of pre-marketing and post-marketing clinical trials in collaboration with proprietary pharmaceutical firms; 3) conduct investigator-initiated studies on PD/PK of drugs in children; and 4) provide an environment in which pediatricians and others can gain supervised experience in pediatric clinical pharmacology." The RFP went on to state, "It is expected that most of the studies.....will be clinical and pediatric". It was clear the intent of the RFA was to fund a network of centers that would conduct clinical research that would ultimately increase pediatric information necessary for labeling of drugs for children. Behind this initiative was the recognition that, in contrast to the adult clinical trial industry, an infrastructure for widespread conduct of pediatric clinical trials did not exist within the U.S. The PPRU Network would form the nidus of such an infrastructure.

The first 5 awards were made in January of 1994 to Louisiana State University (LSU) in Shreveport, Columbus Children's Hospital, University of Tennessee/LeBonhuer Children's Medical Center, the University of California at San Diego, and Wayne State University/Children's Hospital of Michigan. Within the first year of the network, two additional sites were funded, University of Arkansas for Medical Sciences/Arkansas

Children's Hospital and Case Western Reserve University/ Rainbow Babies and Children's Hospital, to bring the total to 7 sites during the first 5 years of the network. During the second year the Dr. Ralph Kauffman and the Wayne State PPRU moved to Children's Mercy Hospital, Kansas City, Missouri.

The network was funded through the U-01 mechanism with governance by a network steering committee comprised of the PI's from each site and a representative from NICHD. Dr. Sanford Cohen, Detroit, Michigan, was appointed to Chair the Network Steering Committee.

Considerable time and effort during the first 2 years of the network was devoted to developing an organizational structure for the network, creating operating procedures, and determining a strategy for partnering with the pharmaceutical industry while at the same time being an NIH-funded network. It is worth emphasizing that the PPRU network was very different in mandate and intended function from the other NIH networks. The existing networks did not provide useful models for the PPRU to emulate. At the beginning, different individuals had very different concepts of what the network mission should be. In addition, organization and efficiency of the network was hampered during the first 5 years by the lack of a coordinating center to manage organizational and administrative functions. Nevertheless, during the latter half of the first award period, the network function improved as reflected by the increase in productivity during years 3-5.

B. Second Five Years: 1999-2003

As the second five-year period was initiated, the commitment of the National Institute of Child Health and Human Development (NICHD) to the PPRU was both continued and enhanced. The RFA for the second 5 years of the PPRU again recognized the need for clinical studies to support pediatric labeling and drug use information in children. It also acknowledged the continued need for a greater infrastructure for pediatric clinical research.

However, the mandate for the network was substantially broadened with a greater emphasis on innovative translational research relevant to pediatric pharmacology. A primary stated goal in the second RFA, in addition to data to support labeling, was “to investigate the pharmacology of new molecular entities and biopharmaceuticals for use in children”. The RFA included 5 specific aims: 1) “conduct of studies in bioavailability, formulation, drug metabolism, PK, PD, safety and effectiveness of drugs” ; 2) “accrual of clinical data necessary for pediatric age-specific labeling”; 3) “molecular approaches, application of new technology, pediatric formulations, validation of new endpoints or surrogate markers”; 4) “research on developmental characteristics and genetic polymorphisms of drug metabolizing enzymes, PK modeling, and simulation technology”; and 5) “provide a teaching environment”.

In the second five years of the network, the seven original sites were refunded and six new sites were added to the network for a total of 13. The new sites were Baylor College of Medicine/Texas Children’s Hospital, Cincinnati Children’s Hospital Medical Center, Wayne State University/Children’s Hospital of Michigan, Children’s Hospital of Philadelphia, National Jewish Hospital/Denver Children’s Hospital, and Yale University. The addition of six new centers to the initial seven centers expanded the pool of clinical pharmacologists involved with the PPRU and added several important pediatric specialties. These disciplines included: Hematology, Oncology, Pediatric Psychiatry, Endocrinology, Allergy/Immunology, Neonatology, Nephrology, Emergency Medicine, and Pulmonology. This increased the breadth of studies proposed and conducted as well as the number of children who could be enrolled in studies.

The organization and governance of the network remained essentially the same for the second funding cycle. Dr. George P. Giacoia of the Endocrinology, Nutrition and Growth Branch, Center for Research for Mothers and Children of NICHD remained as Program Director. Dr. Cheston Berlin, Professor of Pediatrics, Pennsylvania State University School

of Medicine, Hershey, PA, was appointed Chair of the Network Steering Committee to replace Dr. Sanford Cohen. Dr. William Rodriguez from the Food and Drug Administration was appointed FDA Liaison to the Network.

With the expansion of the network, organization became more complex, leading to modification of committee structure and expansion of standard operating procedures. During the 6th year, a contract with Kunitz and Associates, Inc., was signed to develop a Network Operations Center to coordinate organizational and administrative functions. This was a major advance in improving the operations of the network. Operations improvements during the second 5 years included real time online data reporting via a secure web site. For the first time this provided systematic centralized collection of network performance data and protocol coordination. In addition, a web site was designed and placed on-line.

The current organizational structure of the network is depicted in Figure 1 (Appendix A).

III. Key events in the history of the PPRU and the impact of external events

The accomplishments of the PPRU network under the second RFA occurred within the context of several major events in the biomedical community that directly or indirectly impacted the mission of the network.

A. 1994 Pediatric Rule

In 1994 the FDA promulgated new regulations intended to facilitate pediatric labeling. Among other things, the 1994 regulations provided that adult efficacy data could be extrapolated to children if the condition for which the drug is intended was substantially the same in adults and children. These regulations also established the Pediatric Committee within CDER and the “Pediatric Page” which required sponsors and the FDA to identify early in a new drug’s development if it had anticipated use in children and, if so, what pediatric

studies were planned. The 1994 rule had a very modest impact on pediatric studies, although the Pediatric Committee did provide an avenue within CDER to advocate for pediatric issues.

B. 1998 Pediatric Rule

In 1998 the FDA finalized a new regulation that for the first time required new drugs and some marketed drugs to be studied in children if the drug offered significant health benefits for children. This regulation did not go into full enforcement until December, 2000. It is somewhat premature to judge the full impact of the 1998 rule, but it certainly has had the effect of causing sponsors to develop pediatric clinical research plans earlier in the course of new drug development. This has significantly changed the culture in both the FDA and the pharmaceutical industry to stimulate the consideration of pediatric studies as an integral part of new drug development planning.

C. 1997 FDAMA

The passage and implementation of the pediatric exclusivity section of FDAMA had the most dramatic impact on drug research for children and on the activity within the PPRU during the past 5 years. Section 111 of FDAMA provided six months additional exclusivity for a drug if the company performed pediatric studies in compliance with a request from the FDA. The industry responded to this incentive to an unprecedented extent. Five hundred sixty-eight studies were requested by the FDA. By early 2002, 75 studies had been completed. More than 53 drugs were granted additional exclusivity and pediatric labeling was added to 31 drugs at the time of this report. The increase in sponsored pediatric studies created an exponential increase in PPRU activity that would not have occurred without this legislation. As non-PPRU pediatric study sites evolved in response to FDAMA, the PPRU found itself increasingly playing more of a specialty role in being a resource

primarily for phase I & II and PK/PD studies while non-PPRU study sites played an increasingly greater role in phase III & IV studies. The PPRU might not have had this opportunity, at least not in the short time frame, had the FDAMA stimulus not been present. The statistics arising from FDAMA and the role of the PPRU are detailed below.

D. Best Pharmaceuticals for Children Act

The Best Pharmaceuticals for Children Act (BPCA), signed into law in January of 2002, reauthorized the 6 month additional exclusivity provisions of Section 111 of FDAMA. In addition, this legislation added several new provisions that will have important implications for the PPRU during the next five years. The more important additions are summarized below.

1. Within one year of passage, BPCA requires the NIH in collaboration with the FDA to publish a prioritized list of: a) drugs with an approved NDA; b) drugs with an application under review; c) drugs with no patent or exclusivity protection (off patent drugs); and d) drugs referred to the NIH for study under section 505A(d)(4)(C) of the Act. For each drug on one of the lists the FDA must consider, among other things: 1) whether new pediatric studies may produce health benefits for children; and 2) whether reformulation for pediatric use is necessary.
2. The NIH may issue contracts to third parties to do pediatric studies if sponsors of “off patent” drugs decline to do studies in response to an FDA-issued letter of request. If studies are done under this provision, results of studies and requested labeling changes are to be made public. Labeling disputes between sponsor(s) and the FDA may be referred to the Pediatric Advisory Sub-committee. Refusal of a sponsor to accept labeling changes may cause a drug to be declared misbranded. This particular provision is a potent enforcement tool to encourage pediatric labeling changes.

3. The statute establishes a fund in the NIH Foundation to fund studies of “off patent” drugs for which the FDA issues a letter of request and no sponsor agrees to fund the studies. \$200 million are authorized the first year to fund studies, although no appropriation exists to date to fund the authorization. The foundation also may accept donations from private entities to fund studies.
4. There is a new emphasis on neonatal studies to stimulate studies in newborns where appropriate.
5. There are requirements for detailed reporting to Congress by the FDA within 5 years of passage regarding the impact of the law.
6. There are new requirements for adverse event reporting for studies conducted under the BPCA.
7. The Institute of Medicine is required to conduct a complete review of all federal regulations pertaining to research involving children and report to Congress within two years.

E. Human Genome Project

In the spring of 2001, the “completion” of the Human Genome Project was announced, including the public project led by Francis Collins, M.D. and the private project led by Drs. William Hazeltine and Craig Venter. Several surprises emerged: the number of genes (35,000 to 40,000) was far smaller than the original 100,000 predicted; alternative splicing was far more important than originally perceived, and the magnitude of single nucleotides polymorphisms (SNPs) began to be fully appreciated.

F. Functional genomics and bioinformatics

A third advancement is the ongoing expansion of the fields of functional genomics, bioinformatics, and proteomics. With gene chips containing between 5,000 and 30,000

genes/chip, factors that both up-regulate and down-regulate specific genes can be rapidly identified. Because of alternative splicing, a given gene may encode a variety of proteins and the science of proteomics is necessary to define these. The field of bioinformatics is essential to interpreting the complex information generated by these techniques. These technologies and new areas of knowledge will markedly expand the potential of pharmacogenomics, receptor biology, and molecular pharmacodynamics.

IV. Implications for the Future

Several aspects of the BPCA have particularly important implications for the PPRU during the next 5 years. Based on the past five years' experience, reauthorization of the extended exclusivity provision ensures a growing demand for clinical studies in all age categories. Added to that is the impact of the requirement for studies of selected "off patent" drugs, in which the PPRU is expected to play a major role, particularly in PK/PD studies, drug metabolism studies, and relevant translational research. Studies of "off patent" drugs will require considerable participation of the PPRU in prioritization of drugs to be studied, design of protocols, and conduct of studies, thereby markedly increasing demands on the network. The new emphasis on neonatal studies presents unique challenges around ethics, logistics, innovative age-related outcome measures, unique newborn indications, and formulations for the neonatal population. These increased demands will occur in the context of critical review and increased scrutiny of research ethics. All of these factors will increase the workload demands on the network while increasing the complexity of the clinical research environment.

The rapid advances in genomic techniques and emerging proteomics technologies present unprecedented opportunities to advance knowledge about the regulation of drug disposition, changing response to drugs during growth and development, and etiologies of severe adverse reactions to drugs. The network must be prepared to exploit these

disciplines and technologies in the continuing effort to understand age-dependent responses to drugs.

V. Specific Aims of the Original RFA (1994 – 1998)

A. Accomplishments in meeting specific aims

From 1994-1998, seven academic medical centers constituted the Network. These provided access to disparate pediatric sub-specialists and an estimated 160,000 inpatient admissions and 2.3 million out-patient visits per year.

As previously mentioned, the PPRU grant provided funding for the infrastructure necessary to support the goals of the network. The NICHD funded PPRU sites via a cooperative agreement wherein the institute and each site partnered to set and evaluate goals for the research. Funded personnel included a Pediatric Pharmacologist (25%), Associate Clinical Pharmacologist (50%), Nurse Coordinator (100%), data coordinator (25%), secretary (25%), lab director (25%) and technician (50%) for a maximum of 3 FTE's. Sites were expected to fund the remainder of individual salaries through institutional, grant and contract sources. A modest supply and equipment budget was provided with an expectation of augmentation from other sources. For governance, each site PI, the NICHD program officer and a chairman, selected from a non-PPRU site, constituted the Network Steering Committee (NSC) that met quarterly and held biweekly conference calls. These were the major resources and components of the PPRU Network, and accomplishments should be viewed accordingly. Because the Network Operations Center (NOC) was not funded until the second five-year cycle, global data regarding the accomplishments of the PPRU during the first 5 years are difficult to collate. As a result, a selection of accomplishments will be reviewed.

B. Review of the Program Impact

As mentioned, there was no specific organizational structure within the NICHD after which the PPRU could be modeled. As a result, considerable time and effort was spent developing an organizational structure and governance mechanisms at the same time the scientific agenda was advanced. The PPRU network was built where no paradigm previously existed. The RFA allowed for network protocols, which were conducted at more than one site, and local protocols, which were conducted at only one site. The latter group was developed to encourage sub-specialty investigators at individual sites to cooperate with the PPRU and in return, the resources of the PPRU were available to support research that met the aims of the network. Because the legislation that enabled a dramatic increase in pediatric labeling studies was not enacted until late in the first five years of the PPRU, many of the network and local protocols were investigator-initiated and not funded by the pharmaceutical industry.

Noteworthy investigator-initiated studies completed during this time included:

- evaluation of CYP3A4 ontogeny in infants and children
- hepatic drug metabolism (CYP1A2/NAT2) in CF
- meropenem PK in patients with CF
- PK of pentoxifylline in patients with sickle cell anemia
- PK of famotidine in children with acute and chronic renal failure
- antigenic biomarkers of acetaminophen toxicity
- ontogeny of CYP2D6 in the first year of life

Despite the lack of incentives for pharmaceutical manufacturers to perform pediatric labeling studies until late in the first cycle of the PPRU, the PPRU was involved with many studies that were industry-sponsored. Among these were:

- GHRF in hypothalamic growth hormone deficiency
- PK of intravenous liposomal Nystatin

- PK/PD/safety/efficacy of Meropenem in CF
- PK of Linezolid in infants and children
- PK of Prucalipride in constipation/obstipation
- PK/PD of Cisapride in preterm neonates
- PK/PD/safety/efficacy of Ridogrel in ulcerative colitis
- PK/efficacy/safety of oral ranitidine
- PK/PD/safety/tolerance of IV propacetamol
- PK of Metformin in pediatric type II diabetes mellitus

In addition, the PPRU was involved with sponsors who filed New Drug Applications (NDAs) for several important compounds, including:

- Controlled-release APAP (Ascent & McNeil)
- Trovafloxacin IV (Pfizer)
- Midazolam oral solution (Roche)
- Famotidine (Merck)*
- Rifapentine (Hoechst Marion Roussel)**
- Propofol (Zeneca)
- Levofloxacin (Johnson and Johnson)
- Pleconaril (ViroPharma, Incorporated)

* denotes sNDA submitted under 1994 FDA Pediatric Final Rule

** denotes PPRU Local Protocol

The PPRU Network delivered products and services that met the Specific Aims during the first cycle. The impact on overall objectives was difficult to ascertain because the protracted outcomes of off-label prescribing and rational pharmacotherapy of children will only be evident in five to ten years.

As of September 2000 (FDA report to Congress of 1/2001), 25 drugs had been granted pediatric exclusivity and 12 showed newly approved labeling for pediatric use. One may consider that this rapid timeline was enabled by PPRU participation to complete studies. Of the 12 drugs, the Network assisted or performed studies with ibuprofen, midazolam, and ranitidine. Of the 25 granted exclusivity, PPRU involvement included ibuprofen, midazolam, ranitidine, propofol, enalapril, and tramadol. Since exclusivity was granted in year 2000 or before, much of the work done by the PPRU Network is likely to have occurred in the first period. Contributions to pediatric labeling were also evident from publication of data from several PPRU Network studies, including studies of the following drugs: linezolid, naproxen, cefpodoxime, cefotaxime, metoclopramide, pralidoxime, terbinafine, rifapentine, montelukast, pleconaril, cefpirome, and irbesartan.

The contributions of the PPRU also are documented in the medical literature. The list of publications is included as Appendix B.

Furthermore, toward the end of the first cycle, the groundwork was developed to create a model for performing pediatric clinical trials efficiently. Prior to the creation of the PPRU, the pharmaceutical industry already developed successful strategies for conducting clinical trials in children only in selected therapeutic areas (e.g. antibiotics, immunizations, etc.). Major therapeutic areas were largely ignored. The PPRU pioneered the development of study designs and techniques that permitted successful studies in many therapeutic areas that had been previously ignored (e.g. antihypertensives, oral hypoglycemic agents, gastrointestinal agents, etc.). The effects of these “ground-building” efforts are apparent in the surge of industry-sponsored clinical trials during the second cycle of the PPRU.

Furthermore, the PPRU met its educational objectives. The capacity for education and training at each PPRU site is apparent from the credentials of the PIs, institutional support (i.e. statistics unit, specialized laboratories, local collaborators), the number of clinical investigators, and the variety of clinical protocols approved and completed in the

PPRU Network. Sub-specialist participation in protocols was encouraged at PPRU sites during the first period and thereby expanded attractiveness to trainees and faculty. Stable resources which minimized time and effort burdens inherent to clinical research fostered collaboration and hence training opportunities. Several fellows trained at PPRU centers have become significant contributors to the PPRU mission.

VI. Specific Aims of the Second RFA (1999-2003)

A. Accomplishments of the PPRU in meeting the specific aims

During the period of the second RFA (1999-2003), data are available from January 1, 1999 to March 31, 2002 for analysis. An overview of accomplishments during the second funding period may be obtained by examining the number and types of protocols and summarizing other network activities.

- From January to December, 1999, 54 protocols were open; during the year 12 protocols were closed and 42 remained active. Of these 54 protocols, 41 were initiated after January, 1999.
- From January to December, 2000, 73 protocols were open; during the year 17 were closed, and 56 remained active.
- From January to December, 2001, 87 protocols were open, 18 were closed and 69 were still active.
- From January to March, 2002, 76 protocols were open with 66 remaining active and 10 closed.

The dramatic increase in number of protocols during this time period reflects the increased demand for pediatric studies fueled by the extended exclusivity provisions of FDAMA. With respect to types of studies, the PPRU contributed uniquely to a niche area, not typically filled by most pediatric centers, by concentrating on early phase, PK/PD, and

drug metabolism studies. These types of studies require special experience, expertise, and facilities and are more difficult to conduct in children. They entail considerably more translational science in their design and conduct and are essential to the development of appropriate age-dependent dosing recommendations and understanding of drug action in children. Whereas many pediatric health care facilities and practitioners may be capable of conducting phase III and IV studies, the PPRU sites are uniquely qualified to perform early phase, PK/PD, and drug metabolism studies. Over the period January 1999 to March 2002, the majority of studies conducted by the network were Phase I, Phase I/II, or Phase II. Phase III and Phase IV (post-marketing) studies comprised only 17-18% and 4-10% of studies, respectively, annually. In addition, the number of investigator- and network-initiated studies increased during this funding period. The protocols were distributed across a broad range of therapeutic categories and included all age groups. The distribution across age groups was 0-1 month: 16%; 1-2 years: 30%; >2-6 years: 11%; >6-12 years: 11%; and >12 years: 32%. Many protocols included multiple age groups.

In addition to clinical and laboratory-based research, the PPRU network contributed significantly in areas of advocacy and policy. The network developed important advocacy position statements in several dimensions. A number of "white papers" were written on topics such as anti-pyretic drug study design, hypertension, and assessment of pain in infants that were published in well-respected journals. Members of the PPRU Network Steering Committee provided information for congressional hearings and lobbied for bills and regulations to ensure pharmacology research for children. An important development was the establishment of a Web site with links to individual PPRU, FDA, USP, and AAP web sites.

Collaborative linkages were established with Canadian and European Pediatric Pharmacology networks. Two meetings were held with the European Society of Developmental Pharmacology to discuss issues of common interest and explore potential

areas of collaboration. The PPRU has also worked to develop network partnerships with a variety of other NIH networks such as the RUPP, Neonatal, Asthma, and Pediatric AIDS networks.

B. Review of the Program Impact

Network productivity specifically related to RFA mandates for the second funding period are detailed below.

Specific Aim 1: Studies of bioavailability, formulations, drug metabolism, PK, PD safety and effectiveness (SE) of new drugs and drugs already on the market

The majority of clinical studies conducted during the second funding period were responsive to specific aim 1. Sixty-seven to 71 percent of the studies during respective years were primarily PK or PK/PD studies. Four to 11 percent of studies included safety and efficacy data along with PK/PD data. Studies that were only safety and efficacy (usually phase III studies) comprised 11% to 20% of studies in any of the 4 years. "Other" studies comprised 14%, 10%, 7% and 11%, respectively, during the four reporting years of the second funding cycle. Most of these latter studies examined specific aims 3 and 4 and include developmental characteristics of drug metabolizing enzymes. Several types of PK studies were conducted, including single dose oral, single dose IV, multiple dose oral, multiple dose IV, single dose inhalation, topical and single and multiple dose oral/IV.

Specific Aim 2: Age Specific Labeling

The trends in protocol study populations by age group during the second funding cycle reveal an impressive increase in evaluation of children less than 12 years. This represents the age group traditionally excluded in pre-PPRU trials. During the 4 reporting periods, children under 1 month comprised 7%, 8%, 16% and 17% of patients; from one month to two years were 15%, 22%, 30% and 29% of children; from 2 to 6 years were 23%, 23%, 10% and 10%; from 6 to 12 years 29%, 26%, 12%, and 12%, and adolescents 26%,

21%, 33% and 33%. Many of the studies in children over 12 years of age were in patients with hypertension; diabetes mellitus type II and other age-specific disorders.

Specific Aim 3: New Therapeutic Modalities

The range of therapeutic classes of drugs examined under the second RFA was far broader than under the first RFA. This reflects, in part, the stimulus of FDAMA and the expanded expertise and patient populations within the network. The therapeutic classification of drugs studied included analgesics, anti-infectious agents, anti-hypertensives, anti-diabetics, anti-histamines, antipyretics, GI drugs, hormones, hormone/hormone antagonists, psychiatric/behavioral disorder drugs, anesthetics, anti-inflammatories, topicals, sedatives, and anti-epileptics. Anti-infectives was the most frequent therapeutic classification represented, with testing of anti-virals, antibiotics, and antifungal agents. Antihypertensives and GI drugs were typically the second and third most studied categories, respectively.

Specific Aim 4: Developmental Characteristics of Drug Metabolizing Enzymes, PK Modeling, and Simulation Technology.

A trend in the development of protocols, indicates an increase in investigator developed protocols. In the years January to December, 1999, and January to December, 2000, fully 75% and 71% of protocols were sponsor or sponsor/investigator designed. From January to December, 2001 and January to March, 2002, 35% and 47%, respectively, were investigator designed or PPRU and other Federal agency co-designed. Pharmacogenetic studies, and studies of ontogeny of drug metabolizing enzymes figured prominently in these investigator designed studies. More recently, 3 major network initiated projects have been developed and either have been or will be submitted for NIH funding. (See Section VI below.) These include study design modeling and PK modeling.

Specific Aim 5: Education.

The educational activities of the PPRU were focused in three main areas:

- training and improved communication between Coordinators at each site;
- training of Associate Pharmacologists, who develop competency in Clinical Pharmacology as well as their primary pediatric specialty;
- Mentored Specialized Clinical Investigator Development Awards (MSCIDA) Grants for Pediatric Clinical Pharmacology Fellows using the K-08 NIH funding mechanism.

During the second funding cycle 13 Associate Pharmacologists are in training across the network. From 1/1/97 to 8/1/01, 25 fellows were in training at network sites. The network currently is developing a common fellowship curriculum to be employed throughout the network.

C. Summation:

In the second five-year period of the PPRU's existence, all five specific aims of the RFA have been successfully fulfilled. All 13 sites have contributed to the success of the network. The number of protocols active at individual sites ranged from 7 to 22 protocols in year 1999, 7 to 28 protocols in 2000, 12 to 33 protocols in 2001, and 7 to 15 protocols in the first quarter of 2002. The trend in PPRU and non-PPRU participation has shown an increase in PPRU exclusive and single-center exclusive studies from 52% in 1999 to 69% in 2002. In particular, the past four years have been successful from the perspective of drug testing in children, studying a wider array of medications and younger age groups. Furthermore, there has been a substantial increase in network-initiated studies and integration of translational science into the protocols. The network also is fulfilling an essential mandate to train the next generation of experts in pediatric pharmacology.

VII. Responsiveness of the PPRU in meeting changing opportunities

Over the first nine years, the PPRU has evolved and continues to evolve and mature. While significant progress has been made in a number of areas, many challenges remain. Therapeutic areas that have not received adequate attention include disordered sleep, hyperlipidemia, contrast imaging agents, and many psychiatric disorders. Furthermore, alterations in drug distribution, metabolism, disposition, and elimination that are unique to pediatric subpopulations (e.g. neonates) remain to be determined for many important therapeutic agents. Comparative trials, to determine optimal therapy when more than one agent is available to treat a disorder, are fertile ground for further investigation. Drug-disease interactions and the effect of therapeutics in children with multiple diseases have been studied extensively for selected conditions (e.g. cystic fibrosis) but not others (e.g. diabetes mellitus, nephrotic syndrome). Differences in responsiveness (e.g. pharmacodynamics) need to be elucidated for many conditions in children (e.g. hypertension). Drug formulations appropriate for children who are unable to swallow capsules and tablets remain a critical issue for pediatrics. New agents developed from basic research in proteomics and immunology will need to be evaluated in children. Finally, it is conceivable that the risks of biological and chemical warfare may impact the future of the PPRU. To accomplish these goals, new study designs and methodologies will need to be adapted from adult trials or created de novo. It is clear that meeting the changing needs of pediatric patients is an ongoing challenge, one that will require maintenance of the infrastructure necessary to meet new therapeutic needs and opportunities.

To test this network evolution, the PPRU has developed a new model for advancing therapeutics in areas that have previously been understudied. Several projects have been developed to test the ability of the network to focus diverse resources on a common target. To meet these challenges, a PPRU Research Committee was developed. It was chaired by Dr. Stanley Szeffler the first year of existence and Dr. Ralph Kauffman during the second

year. This Committee identified key areas of interest for the PPRU and identified Working Groups to develop network-initiated protocols. Each Working Group is composed of representatives from all PPRU sites. The Working Groups meet regularly via the Steering Committee meetings and conference calls to develop research plans and protocols. At the present time there are five functioning Working Groups. Accomplishments and current activity of these Working Groups include:

1. Psychopharmacology

The rationale for forming this Working Group was the critical need for pharmacokinetic, pharmacodynamic, and safety information for many drugs used in psychopharmacology. We chose to focus initially on atypical neuroleptics used in children and adolescents with autism and other pervasive developmental disorders (PDD) as it would allow for collaboration and synergy with a sister institute (NIMH) and a network, RUPP, with a mission very similar to our own. The frequency of risperidone use appears to be high in this population as estimated by a survey performed by members of the RUPP network. Of the 417 respondents to the survey 11.8% of children were taking antipsychotics of which risperidone represented 87% of all mentions. Given the tender age and potential vulnerability of this population at neuroleptic initiation, as well as the likelihood that therapy will be chronic, typically spanning many decades, the dosing ranges, safety and validation of therapeutic utility of drugs such as risperidone for PDD must be established. The critical need for proper studies in this vulnerable patient population was further emphasized by a RFA that called for development of innovative treatment approaches to autism (NIH, Nov 1999).

Over a period of about 8 months, this working group developed a clinical multi-center protocol to study the population pharmacokinetic of risperidone and metabolites in children with PDD. The objectives are to adapt and establish micro-assay methodology sufficiently

sensitive for pediatric sampling (Assays are being set up at the LSU, Shreveport (John Wilson) and the laboratory of Sander Vinks, at the Cincinnati PPRU site) and to prove feasibility of RIS and 9-OH-RIS enantiomeric determination in samples from pediatric PDD patients that will enable full population-PK characterization in children with PDD. A secondary focus of the study is to gather (preliminary) pharmacodynamic data relating EPS adverse event data to RIS metabolism/ elimination.

The Working Group worked hard to complete the proposal in time to submit an application for funding to NICHD in response to the RFA for studies in this area. All of the Centers within the PPRU and RUPP Networks agreed to participate, with Cincinnati as the Lead Site and Data Coordinating Center for the study. Clinical protocol and informed consent forms are currently under IRB review at most centers. The lead site has identified its first patients, and enrollment is expected in due course.

Patients will be studied for 2 years and the results will be used as preliminary data for a comprehensive application that will apply the Extreme Discordant Phenotype (EDP) approach to look at drug factors which are key to the way risperidone works: mechanism of action and safety. By using EDP methodology, we will define RIS response variability and adverse events sensitivity by studying pharmacodynamic-pharmacokinetic response and pharmacogenetic information of either its metabolism/elimination pathway (CYP2D6, 3A4) or presumed site of receptor activation (dopamine and serotonin (5-HT) receptors and transporters). We currently are in the process of planning the application (R01) while collecting additional data on patterns of extrapyramidal symptoms and distribution of populations exposed to risperidone in the age group 5-<18 year to further characterize the dose-concentration-response/AE relationships.

Other areas of interest to this working group include: 1) ADHD treatments with a draft investigator initiated protocol submitted by Dr. John Wilson (LSU). This protocol is being finalized and funding is pending; 2) The proposal developed by the Diabetes and

Depression working group (see below), offers potential for development of additional protocols modeled from and spinning off from that study. An R01 application has been submitted for consideration; 3) Neuroprotection following a traumatic, environmental, metabolic or infectious CNS insult remains an interest but at present only site specific projects are available to model. Dr. Sander Vinks participates in an NIH supported project “A randomized controlled trial of amantadine for arousal in pediatric traumatic brain injury, a pilot study.” If initial data from that trial are encouraging, the network may rollout a larger study based on part of this work. The long-term goals of this work group are to secure pilot and RO1 funding in novel or “risky” projects which are unlikely to receive industry support in as many areas of psychopharmacology that can be supported by the expertise of the respective PPRU network sites.

2. Diabetes and Depression Working Group

The rationale for forming this group was that depression is much more common in youth with type 1 diabetes (T1DM), that the presence of depression adversely impacts on treatment of diabetes leading to poor diabetes control, that poorly-controlled diabetes is likely to influence the bio-disposition of psychopharmacologic agents, and that there are no data currently available concerning psychopharmacologic management of depression in diabetes. The fact that NIDDK identified the co-morbid occurrence of depression and diabetes as an area in need of further study made the rationale for this group even more compelling. Over a period of about 18 months, this working group developed a comprehensive clinical pharmacologic study proposal examining the use of paroxetine (PXT) in depressed youth with T1DM.

The overall objective is to determine if effective treatment of depression results in long-term improvement of glycemic control of T1DM in youth who are affected by both conditions. A series of 3 successive, interdependent studies will be conducted by all of the centers in the PPRU Network. Study Phase 1 will determine if the degree of metabolic control of diabetes

(based on levels of HbA1c, fructosamine, and continuous glucose monitoring), age, and CYP2D6 genotype influences the pharmacokinetics (PK) of PXT. Study Phase 2 will determine the efficacy of PXT over 12 weeks in placebo non-responsive T1DM youth using dose recommendations determined in Study Phase 1. The influence of anti-GAD antibodies on psychiatric responses and the effect of PXT treatment on the HPA-axis, diabetes quality of life, and compliance with therapy will be explored. Population PK analysis integrated with pharmacodynamic assessments will be performed to refine/confirm dose predictions from Study Phase 1. Study Phase 3 will be the pivotal, randomized control study that will determine the long-term benefits and risks of PXT therapy in depressed diabetic youth. In this Study Phase, depressed youth with T1DM will be randomized to either PXT or placebo in a double blind manner and patients will be studied for 1 year. The results of these studies will categorically determine the influence of effective treatment of depression on long-term control of T1DM.

The Working Group was able to complete the proposal in time to submit an application for funding to NIDDK in response to the RFA for studies in this area. All of the Centers in the PPRU Network agreed to participate and KAI will serve as the Data Coordinating Center for the study. The proposal was approved but not funded and will be resubmitted in February of 2003.

3. Neurology Working Group

Dr. Adamson from the Children's Hospital of Philadelphia site is leading this working group. This is a joint collaboration with a working group of pediatric neurologists led by Dr. Tracey Glauser from The Children's Hospital Medical Center of Cincinnati. A collaborative protocol to study childhood absence epilepsy (CAE) is being developed for NIH grant submission. The proposal has been encouraged by NINDS.

The protocol in development will be a multicenter, randomized, double blind comparative study of the effectiveness of ethosuximide, valproic acid and lamotrigine monotherapy in pediatric patients with previously untreated childhood absence epilepsy. The trial will determine

the most effective monotherapy between ethosuximide, valproic acid and lamotrigine for pediatric patients with childhood absence epilepsy; determine if interpatient variability in drug disposition underlie the variability in clinical response and toxicity observed in pediatric patients; and define whether there is a pharmacogenetic basis to the drug induced weight gain observed in children treated with valproic acid.

The working group will utilize expertise from throughout the PPRU in designing this protocol. Drs. Michael Reed and Jeffrey Blumer at Rainbow Babies And Children's Hospital's research laboratory will perform the drug analyses for the pharmacokinetic studies. Dr. Capparelli at the University of California, San Diego in conjunction with Dr. Vinks in Cincinnati will be performing the population modeling for the three anticonvulsant drugs under study. The Biostatistical Support will be provided by Drs. Cnaan (Children's Hospital of Philadelphia). Pharmacogenetic studies will be coordinated by Drs. Kearns and Leeder (Children's Mercy Hospital) in collaboration with investigators at The Children's Hospital Medical Center of Cincinnati. EEG analyses will be coordinated by Dr. Dennis Dlugos at the Children's Hospital of Philadelphia.

This trial would be the largest trial conducted in children with CAE, and provide highly relevant information for the care of children with this common childhood disorder.

4. Pulmonary, Allergy and Immunology

The leader of this group is Stanley J. Szeffler, M.D. from the Denver PPRU. This Working Group has centered its attention on the evaluation of medications for the treatment of childhood asthma, especially for use in young children. The Working Group initially gained experience in asthma research by conducting protocols with pharmaceutical sponsors (Astra Zeneca, Glaxo Smith Kline, Merck) who sought labeling of the following medications, inhaled steroids, leukotriene antagonists, and short acting bronchodilators. In addition, the PPRU conducted a pharmacokinetic evaluation on a new class of medications, phosphodiesterase 4

inhibitors (Byk Gulden). Studies are currently being conducted with PPRU participation in the evaluation of inhaled steroids down to age 6 months. Dr. Gregory Kearns (Kansas City) has provided core expertise in the area of pharmacokinetics, along with Dr. Edmund Capparelli (San Diego) in population pharmacokinetics, and Dr. Jefferey Blumer (Cleveland) in assay development. All of this provides experience and preliminary data for the design of network-initiated studies.

In addition, studies have been conducted on the pharmacokinetics of antihistamines for the treatment of allergic disorders down to age 1 year (Aventis). This Working Group has also formulated protocols for the evaluation of inhaled steroids for the prevention and treatment of bronchopulmonary dysplasia.

The PPRU network is also conducting studies on the pharmacokinetics of inhaled steroids in collaboration with the NHLBI Asthma Clinical Research Network to determine whether differences in systemic absorption influence systemic effect and efficacy. Dr. Blumer's PPRU laboratory at the Cleveland site is conducting this analysis, which should shed light on the application of pharmacokinetics in the evaluation of poor response to inhaled steroids. Opportunities are available to bridge NIH network studies with the NHLBI Childhood Asthma Management Program and the NHLBI Childhood Asthma Research and Education Network, as well as continuing collaboration with the NHLBI Asthma Clinical Research Network.

The Working Group is currently designing network-initiated studies to evaluate the efficacy of inhaled steroids in young children. This age group represents a major challenge related to medication delivery, as well as the assessment of beneficial and systemic effect. This set of studies will attempt to incorporate several biomarkers to determine whether they can be used to predict response to inhaled steroids.

Based on the success of the current Working Group structure, the Research Committee currently plans to develop additional Working Groups in the areas of hypertension, pain management, and sleep disorders. The Research Committee currently Chaired by Dr. Ralph

Kaufman (Kansas City) anticipates that these new Working Groups will continue to develop network-initiated cooperative studies as a focus of their activity. In addition, they will develop position papers on the work in their respective areas related to the clinical pharmacology of their medication class and the methods of conducting pharmacokinetic, safety and efficacy studies in the relevant age groups.

5. Neonatal Working Group:

The Neonatal Working Group, chaired by Dr. Jack Aranda, developed a strategic plan to address key issues in neonatal pharmacology. This plan is presented in Appendix C.

Section II: Future Challenges: Assessment of the Most Critical Needs within Pediatric Therapeutics

Despite the tremendous progress that has been achieved during the past two decades, many important issues remain to be addressed within the field of Pediatric Clinical Pharmacology and Toxicology. Many aspects of developmental pharmacology, particularly related to the ontogeny of drug metabolism and elimination in the neonate and during puberty are incompletely understood. Despite significant advances in pediatric labeling, many drugs still lack formulations suited to younger children and children with severe developmental disabilities. Many of the outcome measures used in studies conducted in adults, such as the effects of treatment on mortality related to hypertension and renal failure in diabetes mellitus, are impractical if not impossible to apply to the pediatric population. Furthermore, developmental changes unique to children and the practical and ethical demands in pediatric research require new methods to assess the effectiveness and safety of therapeutic interventions. This necessitates development and validation of new clinical research methodologies, biomarkers, and surrogate markers. Translation of the advances in basic genetics into rational treatment for inherited and autoimmune diseases holds promise for many children who presently have no

effective treatment or effective but highly toxic treatments. Finally, many effective medicines are now off-patent, removing any incentive for industry to complete needed pediatric studies.

As basic scientists uncover critical new information related to the mechanisms of disease, a clear need exists for an organized mechanism to bring the benefits of this research to children. This network was created to improve pediatric therapeutics, a broad and multifaceted mission that requires increasingly specialized skills and cooperation between interested scientists and clinicians. The success of this approach is evident in the aforementioned accomplishments of the network. In the future, increasing cooperation will be needed to bring the promise of more effective and safer therapies to children who suffer from common and uncommon diseases.

The network has tried to identify the most critical anticipated research needs in pediatric therapeutics for the next 5-10 years. The translational and clinical research foci to address these needs have been carefully designed to focus the efforts of the network on areas that:

- are unlikely to be addressed in another way;
- require a high degree of pharmacological expertise resident within the group;
- would be difficult or impossible to conduct at a single site;
- emphasize collaboration with other research groups or organizations in the development of a rational plan for drug assessments in children;
- require unique approaches to meet practical or ethical challenges; and
- have the greatest potential impact on understanding and improving child health.

The areas that have been identified and will be discussed in greater detail include;

- Neonatal pharmacology, including premature infants;
- Developmental pharmacology, pharmacogenetics, and pharmacogenomics;
- Pediatric formulations;

- Research methodology, biomarkers, surrogate markers, and therapeutic outcome measures;
- Population pharmacokinetics, pharmacokinetic-pharmacodynamic modeling, and simulation strategies;
- Molecular therapies, proteomics, and immune modulation of pediatric disease;
- Studies of off-patent drugs for children.

Section III: Proposed Objectives to Meet Current and Anticipated Needs in Pediatric Therapeutics – Future Role of the PPRU

I. Mission Statement and Objectives for the PPRU

The overriding mission of the PPRU is to develop and disseminate new information that facilitates drug development and improves drug therapy for children. The PPRU will actively pursue this mission by focusing on five major goals:

6. Multicenter clinical trials leading to pediatric labeling for drugs, biologicals, and medical devices;
7. Collaborative clinical research that improves pediatric therapeutics but may not lead to pediatric labeling;
8. Translational research that leads to a better understanding of any aspect of drug delivery, disposition, effectiveness, and safety in children;
9. Novel clinical research methodologies in pediatric clinical pharmacology;
10. Training in pediatric clinical pharmacology for health care professionals.

To achieve these goals and to function effectively and efficiently, the PPRU will maintain and continuously improve its organizational structure, policies, and standard operating procedures, data collection and management, as well as communication between sites, the NICHD, and the coordinating center. The PPRU will operate in an ethical manner and the safety of research subjects will be of paramount importance. A review mechanism

is in place such that all studies conducted by the PPRU are reviewed thoroughly. At a minimum, all studies conducted under the auspices of the PPRU will be reviewed for importance of the research question, adequacy of study design, adequacy of subject numbers, methods of data collection and analysis, and subject safety.

II. Justification for the Proposed Objectives

A. Pediatric Labeling: PPRU sites will be expected to participate in clinical trials funded by industry or other sources whose major purpose is to achieve pediatric labeling for drugs not currently labeled for use in children. Despite improvements over the past several years, many drugs that are widely used and/or of great therapeutic significance to segments of the pediatric population still do not have pediatric labeling. Information contained in the label is reviewed and sanctioned by the U.S. Food and Drug Administration and forms the core knowledge necessary for safe and effective use of drugs in the population. The PPRU will continue to play a critical role in advising study sponsors and federal agencies which drugs should be studied and how these studies should be designed and conducted. As novel drugs, drug delivery systems, biological compounds, genetically engineered therapies, and devices are brought to market, the PPRU will play a key role in study design, conduct, analysis, and publication of results. Furthermore, through the Best Pharmaceuticals for Children Act of 2002, older, off-patent drugs that are widely used in pediatric practice will be studied. The PPRU will likely play a central role in the design, analysis, and conduct of these studies. It is this role in study development and design, data analysis, novel clinical research techniques, and dissemination of information that differentiates PPRU sites from sites whose primary function is limited to enrollment of subjects. This type of leadership facilitates the successful completion of studies and ensures that the goal of pediatric labeling is met.

B. Collaborative Clinical Research: Collaborative clinical research that improves pediatric therapeutics but may not lead to pediatric labeling is critically important. Because the FDA requires a very basic set of information to demonstrate effectiveness and safety of an individual drug in the pediatric population, few comparative trials are done to determine which drugs, alone or in combination with other therapies, offer the best treatment for a disease or condition. As a result, treatment for many pediatric conditions relies on anecdotal experience or data from small, poorly designed or controlled studies. There are notable exceptions to this generalization. The NCI and groups such as the Children's Oncology Group have systematically studied combined therapies for cancer in children. The NICHD sponsored Neonatal Network has successfully studied many therapies in a selected population of very young children. And other groups such as NHLBI CARE (Childhood Asthma Research and Education), NAPRTCS (renal transplantation), the ACTG (HIV), and CASG (viral diseases in children), funded in whole or in part by the NIH, have examined optimal treatment strategies for specific groups of diseases.

Although the groups mentioned and others have, with federal support for infrastructure, managed to effectively study therapeutic possibilities in children, many areas of drug treatment have not been singled out for special study. Important therapeutic areas that need to be addressed within pediatrics include: hypertension, epilepsy, gastrointestinal diseases, eating disorders, depression, lipid disorders, pain management, and many others. The PPRU will continue to fill the gaps left between other specific disease focused networks.

In addition to "filling the gaps", pharmacologists often work with other pediatric subspecialty experts on collaborative studies. The field of pediatric clinical pharmacology is almost unique in that it transcends the usual specialty groups by

focusing on drugs used to treat disease rather than a specific disease or organ system. Clinical pharmacology encompasses drug administration, disposition, mechanisms of action, interactions with other drugs and diseases, adverse effects, and comparisons between agents. As a result of this focus, pharmacologists are in a position to offer a unique contribution to therapeutic studies conducted by experts within other pediatric subspecialty fields. Opportunities for collaborative research in which pharmacology plays a critical role in study design, laboratory testing, and data analysis are numerous. Pharmacology may play an important role for comparative therapeutic trials involving drugs with highly variable absorption and disposition, genetic polymorphisms that affect drug metabolism, host factors that affect response, populations where sparse sampling strategies are required, etc. The PPRU will serve not only in an advisory capacity, but will seek to actively involve subspecialty investigators at institutions with PPRUs in collaborative clinical research.

Large, multicenter studies designed to answer significant therapeutic questions are becoming increasingly common. As the size and complexity increases, so does the expense. Because of the monetary and time cost, many large-scale comparative trials will only be done once. The PPRU network brings expertise to these multicenter collaborative studies that in many cases may improve the outcome of the study.

C. Translational Research: Translational research provides the bridge between basic science research and clinical medicine. It makes basic research relevant to therapeutics and improved child health. The PPRU will be involved in translational research that leads to a better understanding of any aspect of drug delivery, disposition, effectiveness, and safety in children. Exciting advances in genomics, proteomics, receptor specificities and functions, signaling, etc. will have a profound effect on the therapeutic options available to future generations. The PPRU will play a

role in the application of basic science techniques developed in areas related to pharmacology to the treatment of specific pediatric diseases.

Because many of the inter-individual differences in drug metabolism and effect are based on genetic differences, and because many of the allelic variants are relatively uncommon, studying drug metabolism and effect in children will require large sample sizes. One of the greatest values of the network is the provision of a potential sample size numbering in the thousands as compared with single sites, which do not have the resources to identify and study an adequate number of subjects. Furthermore, to determine how development affects drug metabolism, effect, and safety, longitudinal studies provide an excellent opportunity to understand these maturational effects. Few if any single centers have the requisite infrastructure and patient population to conduct this type of longitudinal research in children.

The geographic diversity of the network created an opportunity to study specific ethnic subpopulations that are more prevalent in some areas than others. Additionally, for diseases or conditions that are relatively infrequent in the population, multicenter studies are often the only way that adequate numbers of potential subjects can be identified for a study. Furthermore, many diseases or conditions have a genetic basis and therefore become manifest in childhood, often disrupting normal growth and development. Examples of drugs that would have never been studied if not for the network include famotidine in children with renal failure and pentoxifylline. Without the network and its supporting infrastructure, advances in basic research will not be brought to children as quickly or, in some cases, perhaps never.

The undisputable fact that until recently drugs were routinely brought to market without adequate pediatric testing serves as a reminder of the need for a venue to advance therapeutic issues in children. A greater understanding of inter-individual differences in drug metabolism, effect, and safety will help develop specific therapies

that are more effective with fewer adverse effects. It is these changes that are moving the field of pharmacology toward individualized therapy, which ultimately will be of great benefit to children.

D. Novel Clinical Research Methodologies: The development of novel clinical research methodologies to meet the needs of children has long been one of the hallmarks of pediatric research. These novel techniques may take the form of adaptations of monitoring equipment, medical devices, or drug delivery systems. They may involve educational or developmental assessment tools, survey methods, questionnaires, or outcomes measures that differ from those used in the adult population. Or they may involve novel methods to reduce the discomfort or anxiety associated with study related procedures.

To assess the clinical effectiveness or safety of drugs, the endpoints used in adult studies are frequently not attainable or feasible in children. For example, cardiovascular endpoints such as stroke, myocardial infarction, and death cannot be practically applied to pediatric intervention trials. As a result, new surrogate markers that correlate with mortality and morbidity will be required. Biomarkers have proliferated as well, and many of these will be directly applicable, albeit sometimes in a modified form, to pediatric intervention studies.

Because children have developmental and physiological differences, novel methods to study response to therapeutic interventions in pediatric disease will be needed. As new biological and gene-derived therapies emerge and as new non-invasive and invasive monitoring and assessment instruments become available, novel study design and analysis techniques will almost certainly be required. The PPRU will play a role in developing, validating, and testing these new techniques. For reasons previously described, a collaborative network of leading pediatric clinical research

centers focused on pediatric therapeutics will be the most effective way to address these issues.

Finally, many issues surrounding children as subjects in clinical trials or other types of clinical research have become increasingly important. Improving research methodology also must consider these factors. Improving the assent process so that children capable of understanding will comprehend their roles as research subjects is consistent with current social mores and standards of research ethics. Furthermore, methods for studying children involved in interventional research that reduce the risk of exploitation by unscrupulous parents or guardians are important. The issue of using healthy children in research needs to be addressed in a coherent fashion. Because the majority of the research done in the PPRU involves some intervention (generally drug therapy), the PPRU will of necessity be forced to consider these issues.

E. Training in Pediatric Clinical Pharmacology: One of the original missions of the PPRU was to train the next generation of physicians, pharmacists, nurses, and other health care personnel in the principles of pediatric clinical pharmacology. This mission is as important today as it was when the PPRU was originally conceived. As attention has been focused on the disparity between the amount of pharmacological knowledge available in adults vs. that in children, more resources have flowed toward pediatric labeling studies and other “therapeutic intervention” studies. A formal accreditation process has been developed for training programs and in the future, fellowship trained individuals will be required to attend an accredited training program. The PPRU will encourage accreditation of fellowship training programs at individual sites to ensure that individuals interested in pursuing formal training will learn the fundamentals in the field, and, more importantly, will be capable of training future generations.

Outside of formal training programs, the PPRU has a tacit obligation to teach medical, pharmacy, and other students in health care professions the essential principles of pediatric therapeutics.

III. Research Plans

In order to meet the goals set forth above, sites selected for inclusion in the PPRU network will be expected to participate in collaborative research within the network. PPRU sites will also be expected to demonstrate unique strengths that contribute to the overall effectiveness of the network in one or more of the areas outlined under Research Objectives. Furthermore, it is expected that these areas of concentration or strength at individual sites will be accessible to all sites for network approved collaborative research projects or educational programs. It is not expected that each site will necessarily excel at all five objectives. The strength of the network lies in its diversity and in the willingness and ability of the individual sites to take advantage of the strengths available at other sites. Demonstration of meaningful participation in multicenter collaborative research projects is critical to the success of the network.

Because pediatric labeling is critically important, the PPRU will continue to engage in industry-sponsored clinical trials that are expected to lead to labeling. However, the PPRU site and specifically the personnel funded by the PPRU should play a significant role in the design, conduct, analysis, and publication of the results of studies conducted by the network. The PPRU Network Steering Committee (NSC), in conjunction with the Project Officer, has developed guidelines for inclusion of industry sponsored clinical trials as PPRU sanctioned studies. Only those studies approved by the NSC are approved for use of PPRU personnel and resources.

With the passage of the Best Pharmaceuticals for Children Act of 2002, pediatric labeling for off-patent drugs will become a reality. The detailed mechanism by which this will

occur has not yet been announced, but the PPRU is prepared to play a central role in this process. Collaborative clinical research that is not expected to lead to labeling but which contributes to improvements and advances in pediatric therapeutics will remain a goal of the PPRU. This area of research is expected to take on added importance in the network. Because these studies often require external funding that does not come from industry, PPRU resources may be used to develop study protocols prior to approval of the NSC if: (1) the intent is to develop the study for the network, and (2) a brief “concept sheet” and proposed funding plan are submitted for consideration within a reasonable time after the concept is developed. If the project concept is approved for further development by the Research Committee and the NIH Project Officer, then use of local PPRU resources will be permitted as long as the expenses incurred are consistent with the grant application and NIH rules.

It is expected that many collaborative clinical research projects will require funds beyond those granted in the individual awards. Funding for these studies may come from many sources, including: traditional R01 or other NIH funded applications, private industry, private foundations, or, if funded, from a proposed new pool of funds to be allocated for specific PPRU projects. These funds will be allocated through an objective peer-reviewed competitive process. Emphasis will be placed on projects that require multiple sites within the network, those that involve other branches of the NIH or private foundations outside of the PPRU, and those that cannot be effectively done by another existing network. Areas of interest include: comparative studies to determine preferred therapy, developmental aspects of therapy, combined non-pharmacological and drug therapy, etc. The Research Advisory Committee will serve as a control point to ensure that the network remains focused on the stated research goals and objectives and that the resources of the network do not become over-committed.

Like collaborative clinical research, translational research will assume greater significance in the PPRU network. Mechanisms for approval and funding translational research will be similar to those for collaborative clinical research that is not expected to lead to labeling. Areas of interest include but are not limited to: genomics, proteomics, receptors, signaling, gene chip technology, etc. From a funding and approval standpoint, research on novel clinical methodologies will be similar to collaborative clinical research and translational research. It is anticipated that these studies will also play an increasing role in PPRU supported research.

IV. Operational Challenges for the Network

The PPRU was originally configured primarily to conduct industry-sponsored clinical trials that would lead to pediatric labeling. Each site was granted funding divided into relatively fixed categories, with only limited authority to spend funds according to the specific needs of the site. Instead, funds were allocated primarily to salary support, with a modest amount of support for travel, equipment, supplies, and other expenses. It was recognized that conducting labeling studies in children was labor-intensive. As a result, this funding strategy worked reasonably well.

However, the mission of the PPRU clearly is changing. Other non-PPRU pediatric centers have developed the infrastructure to perform clinical trials, particularly Phase III studies that do not involve pharmacokinetic analysis. In the future, the PPRU will not abandon the labeling goal, but more emphasis will be placed on studies developed to answer important clinical questions related to pediatric therapeutics that do not necessarily lead to labeling. This change in philosophy requires a reassessment of the current structure and operation of the network.

First, it should be recognized that the changing mix of studies creates a need for additional study management that was not necessary when industry-sponsored clinical trials

predominated. Unlike industry-sponsored studies, which provide support for study design, study administration, data management, and data analysis, collaborative clinical research, translational research, and research on novel methodologies will require additional resources within the PPRU network for data management and analysis. For non-industry-sponsored studies conducted within the network to be successful, a Biostatistics Core and centralized data management function will be essential. Furthermore, centralized coordination of many network activities will be a priority. Currently, an outside contractor (KAI) supports many critical PPRU functions, including many aspects of information management, data collection and reporting, and assistance with policies and procedures. This function will need to be expanded. Also, outside peer-review of research proposals will increase, creating a need for additional reviewers who will complete reviews in a timely manner and remain available for continued monitoring of safety reports and study outcomes. Coordination of the efforts of the outside reviewers with the activities of the Research Advisory Committee is essential to the timely and successful project review and selection.

In addition, industry-sponsored research projects are closely monitored by Clinical Research Associates (CRAs) employed by or contracted by the sponsor. As the number of projects that are not sponsored by the pharmaceutical industry increases, the need for an appropriate monitoring mechanism arises. Studies not sponsored by a pharmaceutical firm are currently assigned to the PPRU Data Safety and Monitoring Committee (DSMC). Each study must have a Data Safety and Monitoring Plan (DSMP). However, there is limited ability to perform site visits, review source documents, confirm the accuracy of the data, verify that informed consent was properly obtained, and confirm that human subjects' protections were observed. The PPRU needs to develop a monitoring mechanism that provides for both random and targeted review of projects conducted with network approval and involving network resources.

Second, because the scope of the PPRU mission will be broader, additional flexibility at local sites to determine how core funding may be spent will be necessary. In the past, funding has been locked into rigid categories. In the future, the types of research conducted and network resources provided at individual PPRU sites will depend on the unique capabilities at each site. Since it is unlikely that sites will all have the same capabilities, more flexibility will be required so that each site will be able to spend PPRU core funds in the most effective way. For example, if a unit chooses to contribute to the network by providing a core analytical laboratory, that unit may need to fund a full-time research technician. A site that plans to contribute by developing novel research methodology may need to support study design capability that goes beyond that provided by the core network facility. In that case, a laboratory technician would not be needed but expertise in other areas would be required. Justification and accountability are necessary, but flexibility will be necessary to permit effective and efficient allocation of local resources.

Third, additional funding sources will need to be identified. Clinical research obviously is very expensive. Clinical trials sponsored by the pharmaceutical industry and done under an IND application generally provide adequate financial support for clinical costs. Clinical studies funded by sponsors other than private corporate entities typically tend to be funded at less than optimal levels, resulting in transfer of costs to local institutions, patients, and potentially third party payers. Each PPRU site will continue to require adequate financial support for infrastructure (i.e. primarily the people who supervise and work in the local units and related expenses such as photocopying, telephones, etc.). As the emphasis shifts from industry-funded to non-industry funded research, the need for infrastructure support will increase. In addition to this core (infrastructure funding), a mechanism for funding individual studies should be developed. To fund some collaborative studies, PPRU sites may choose to respond to RFAs or prepare RO1 applications. Money from foundations and other private sources may be sought. However, because of the time

required to submit such applications and the competitiveness of the process, it is unlikely that many large-scale clinical studies will be conducted simultaneously. In other words, the money spent on infrastructure will not be utilized effectively as the PI pursues additional funds to support individual studies through traditional funding mechanisms.

To ensure that the PPRU can function efficiently, it will be necessary to provide supplemental funds specifically earmarked for PPRU network studies designed and conducted by the network. There is a clear precedent for this among other NIH-funded networks. If no mechanism for additional funding is provided, the PPRU sites will spend time that could be spent on clinical research instead engaged in attempts to acquire research funding. This likely will result in a reduction in the research output of the network and dilute the effectiveness and potential contribution of the PPRU toward advancing knowledge in this area. In effect, providing money for specific studies will improve the utilization of the core infrastructure supported by the NICHD at each site (i.e. a fixed cost) by reducing the time spent by local PIs searching for additional grant funding rather than engaging directly in research activities. As the mission and focus of the network changes, the funding allocated to the network must also change.

Fourth, the current operational structure used by the PPRU has some inherent inefficiencies, although it has improved noticeably over the past three years. Decisions are made by the Network Steering Committee (NSC). The NSC includes the PI from each of the 13 sites, the Project Officer, and the Chair of the NSC. The NSC holds meetings quarterly for 1½ days. Conference calls, lasting one hour, occur twice each month. The coordinators of each unit, who often spend more time in the day-to-day management of PPRU issues at the local sites, meet annually (1½ days) and have a monthly conference call. Attempts to decentralize workflow by creating subcommittees to manage certain aspects of the PPRU have been partially successful. The effectiveness of the subcommittees has been diluted because they have only limited authority to act. The Network Operations Center (NOC),

currently managed by KAI, has resulted in improved processing of work, improved workflow, better data management, assistance with critical reporting functions, and assessment of network utilization. To become more efficient, decision-making authority will need to be decentralized and a new subcommittee structure based on new network priorities will need to be developed. Professional management should be enhanced and, to prepare for the changing network priorities, a core data management and biostatistical support group, integrated with the services now provided by the NOC, should be developed.

Fifth, as more non-industry sponsored studies are contemplated, improved study monitoring for data accuracy, regulatory compliance, and safety reporting will require additional attention. It would be best for compliance monitoring to be independent from the NIH to avoid a perceived conflict of interest (i.e. monitoring your own studies). Regular reports should be provided for the NIH.

Sixth, as the impact of the Best Pharmaceuticals for Children Act becomes apparent, it will be important to develop an internal structure and procedures to track and expedite these studies. An efficient system will be necessary to meet the needs of the BPCA studies, but until more details of how these studies will be conducted are known, it is premature to speculate how the PPRU should respond.

V. Proposed Organizational Structure and Function

To meet the changing mission of the PPRU and the unexpected opportunities that arise, the organizational structure will need to change. A proposal for modifying the existing structure is shown in Appendix D.

The NSC should be organized so that three primary committees, each with a specific focus, are re-established. These committees are:

- Internal Operations Committee: The purpose of the Internal Operations Committee (IOC) will be to address all matters internal to the network except those related to the acquisition, review, and approval of specific research

proposals. The IOC will continue to prepare, review, revise, and implement network SOPs except for those pertaining to proposal review, protocol review, BCPA, and other procedures that fall under the mandate of the Research Committee. In conjunction with the Research Committee, the IOC will develop a workable and simple policy for authorship. The IOC will have three subcommittees: the Education Subcommittee, the Utilization Review Subcommittee, and the Quality Assurance Subcommittee. The Education Subcommittee, which will replace the fellowship committee, will assume responsibility for the fellowship program and activities plus any other PPRU-related educational activities that occur among the 13 network sites. The Utilization Review Subcommittee will be responsible for monitoring internal network productivity and resource utilization, as has been done in the past. In addition, this subcommittee, with the help of KAI, will prepare an annual report of the accomplishments of the network (publications, other grant awards, number and type of studies conducted by the network, subjects enrolled, etc.). The Quality Assurance Subcommittee will work with KAI, the Project Officer, and the 13 sites to develop and maintain network SOPs related to network QA activities, provide guidance to individual sites, and implement reasonable measures to ensure that research subjects are protected and proper procedures are followed. This subcommittee will not dictate specific policies that are implemented at individual sites, but will verify that adequate SOPs are in place. The QA subcommittee will assist the Project Officer in developing reasonable QA and monitoring plans to supplement the existing DSMC.

- External Operations Committee: The External Operations Committee (EOC) will continue to function as it has in the past. The committee is charged with responsibility for developing and maintaining collaborative relationships with the

pharmaceutical industry, other branches of the NIH, the FDA, professional societies, and organizations whose interests parallel those of the PPRU. If the External Operations Committee (EOC) identifies educational opportunities outside of the network (i.e. collaboration with other networks, sponsored meetings, etc.), the chairs of the Education Subcommittee and the EOC will decide how best to collaborate. The EOC is also responsible for any network promotion or advertising. Finally, the EOC, with help from KAI, will monitor federal and private agencies and help to identify funding sources that may be appropriate for the PPRU to pursue.

- Research Committee: The Research Review Committee (RRC) will address all issues related to the selection, review, and approval of network research projects. The RRC will also encourage and support working groups formed around specific disciplines or projects. This committee will be responsible for assuring that proposals for network studies are reviewed and are deemed to be consistent with the mission of the network. The RRC will also guide the PPRU participation in BCPA projects. The mission of the existing Protocol Review Committee (PRC) falls within the expanded scope of activities to be undertaken by the RRC. Accordingly, the PRC will become a subcommittee of the RRC and will be renamed the Protocol Review Subcommittee (PCS). All industry-sponsored protocols will go directly to the PCS. The RRC will perform the initial review of all investigator-initiated research proposals (concept sheets). Concept sheets that are approved by the RRC will be developed into full protocols, which can then be submitted directly to the PCS. The specific mechanisms and details of the “concept sheet” will be developed by the RRC.

In addition, the RRC will encourage and support working groups that are arranged around a specific pediatric discipline, disease, or an individual research

project. For BCPA projects, the PPRU will need a focused and aggressive response prepared in a timely manner. The RRC is charged with developing such a mechanism, in collaboration with one or more contract research organizations (CROs), and implementing a strategy that will allow the PPRU to play a significant role in studies conducted under the BCPA.

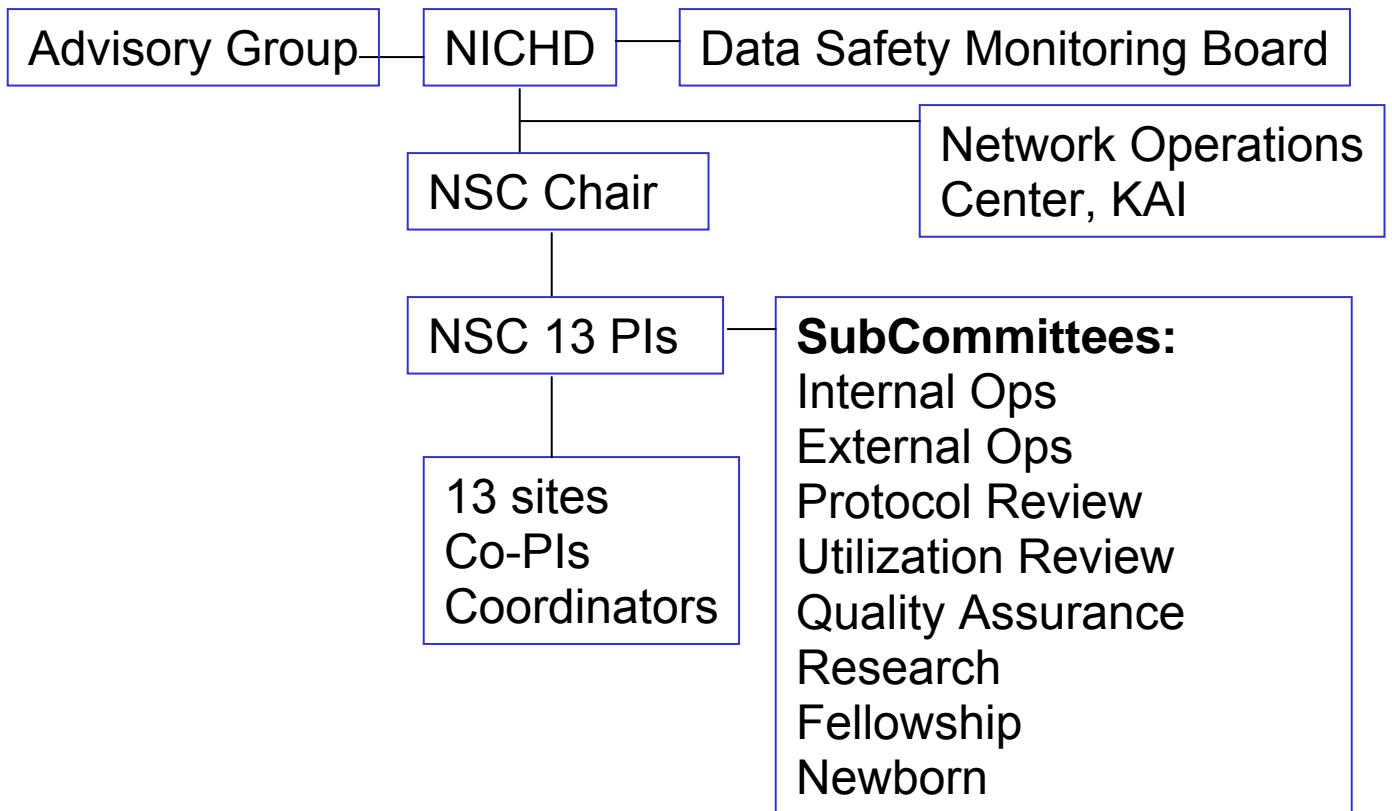
All committees and subcommittees will need greater authority to act in a timely fashion. All “everyday” decisions made by these committees will be conveyed by electronic mail to the NIH Project Director, NSC Chair, and the site PIs, who will be given a reasonable time to raise any objections, after which the decisions will take effect. All significant issues must still be brought before the NSC, either at a quarterly meeting, a regularly scheduled teleconference, or an “emergency” teleconference prior to implementation. The Research Review Committee will be charged with ensuring that the resources available to the PPRU are used to meet specific PPRU goals. The proposed structural revisions are presented in Appendix D.

To allow for useful discussions at the PPRU quarterly NSC meetings, the committee assignments and agenda will need to be carefully crafted so that time can be used efficiently. Strategic planning is an ongoing process. Consideration should be given to forming a small group that considers strategic issues for the PPRU. This group should hold discussions on an ongoing basis. Ideas generated can be brought back to the NSC, discussed, and acted upon in a prospective fashion. Greater use of teleconferences and other technologies to improve communication and workflow between the quarterly NSC meetings is needed.

Finally, the structure of the PPRU requires a strong mechanism for continued communication between sites. The present system is working reasonably well, but consideration should be given to other methods of communicating more information more

effectively. KAI has done an admirable job in coordinating network communications and should be involved in any discussion about enhancing communication between sites.

PPRU Organization Chart 2002



Appendix B: PPRU Publications

1. PPRU NETWORK STUDIES

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STRATEGIC PLANS: PRIORITIES AND NEEDS IN NEONATAL PHARMACOLOGY – 2002

- 1. *Pharmacokinetic data and drug dosing for various birth weight categories and gestational ages in the newborn period.*** The newborn population is a very heterogenous group. Very low birth weight newborns (less than 25 weeks gestational age) receive the most number of drugs in the newborn. They also have the slowest rates of elimination and require different drug dose and/or dosing intervals. Except for the most commonly used antimicrobials, the pharmacokinetic data for most drugs used in the newborn are not available for all levels of fetal maturity or birth weight categories.
- 2. *Pharmacokinetic data, drug dose and dosing intervals for intrauterine growth retarded newborns (also called Small for gestational age or fetal malnutrition..*** Malnutrition is known to significantly influence drug metabolism and disposition. Fetal malnutrition or intrauterine growth retardation or small for gestational age infants is associated with increased neonatal morbidity and mortality. About 20 to 30% of premature newborns also have obviously decreased growth for gestational age. Fetal malnutrition has been suggested to decrease drug metabolism. However, there are no data in newborns to determine the magnitude of the change in drug elimination and individualized drug therapies for this neonatal population.
- 3. *Pharmacodynamic data in newborns of all stages of fetal maturity:*** Drug effects for preterm newborns may vary relative to the term newborns. The receptor sensitivity or receptor number may be very different even among the preterm newborns themselves. For example, the very low birth weight newborns (less than 750 grams at birth) has a high risk of severe hyperglycemia and osmotic dehydration and electrolyte abnormalities due to low basal production of insulin and due to lower insulin receptor number and perhaps affinity.
- 4. *Drugs designed for Unique diseases in newborns:*** The newborns have diseases unique to their state of immaturity. These diseases include respiratory distress syndrome, intracranial hemorrhage, necrotizing enterocolitis, apnea of prematurity, bronchopulmonary dysplasia, retinopathy of prematurity, patent ductus arteriosus, perinatal asphyxia, neonatal pulmonary hypertension and others. Drugs should be developed for these unique diseases since molecular entities designed for adult use may not be appropriate for newborns.
- 5. *Neonatal formulations:*** Many drugs are available only in formulation for adults or older children and must be diluted or prepared for neonatal use. This remains a source of error and substantial cost in newborn drug therapy. Moreover, accurate dosing cannot be ensured particularly when several dilutions are made for newborn use. In sick newborns almost all drugs are given via intravenous route, thus parenteral preparations should be made available for this special population.
- 6. *Efficacy and safety data obtained in newborns:*** These data are often extrapolated from adults or older children. However, all physiologic, and biochemical processes are functionally deficient relative to the older child or adults. Therefore, safety and efficacy should be evaluated in newborns for drugs that will be used in newborns. These studies should include newborns of all stages of fetal maturity (from 23 weeks to 42 weeks gestation) and postnatal ages (1 day to 4 weeks of postnatal life).

7. **Acute and long-term adverse effects:** Drug development should include appropriate studies for acute and long-term effects. Drugs used in the fetus and newborn may cause long-term adverse effects (for example: three-fold increase in cerebral palsy due to postnatal steroid treatment for chronic lung disease, vaginal adenocarcinoma in women exposed to maternal progesterone in the fetal period). Unusual acute adverse effects: (e.g. renal failure, GI bleeding etc) should be explored in newborns whenever these drugs are used for this population. Their effects on drug development and organ function in later life should be included in the drug development plan.
8. **Effects of drugs on Gene Expression in the newborn:** As in number 7, mechanisms underlying the long-term effects of these drugs should be examined. Their effects on gene expression and cell memory should be explored.
9. **Therapeutic superiority studies whenever more than one options are available.** Sometimes there are options for the management of a neonatal disease. Rationale and scientific basis for establishing preferred drugs should be done. Examples of these are: dopamine versus dobutamine, caffeine versus theophylline, surfactant A versus surfactant B, ibuprofen versus indomethacin, etc. etc.....
10. **Fetal drug therapy:** Birth is a transition process that marks the change from fetal state to neonatal state. Increasing evidence indicate that neonatal adverse events e.g. perinatal brain damage and intrauterine infections) may begin even prior to birth. Potential fetal drug therapies (as has been done with antenatal steroids for prevention of respiratory distress syndrome) may be encouraged. Drug therapy for the prevention or amelioration of perinatal damage due to asphyxia should also be examined.

Appendix D: Proposed Organizational Structure (2003-)

