Workshop on Ethical and Regulatory Issues in Global Pediatric Trials
September 21–22, 2009
***Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health**
Office of Pediatric Therapeutics, U.S. Food and Drug Administration
The Legacy Hotel and Meeting Centre, Rockville, MD
Summary of Breakout Group C Discussions

This workshop was sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), U.S. Department of Health and Human Services (HHS), and the Office of Pediatric Therapeutics (OPT), Food and Drug Administration (FDA), HHS, in support of the Best Pharmaceuticals for Children Act (BPCA) Program.

Purpose

The purpose of the breakout discussions was to gather international perspectives on ethical and regulatory issues in pediatric trials. The breakout group discussed three specific topics, answered corresponding questions, identified major issues, and proposed action items/next steps.

Topic 1: Ethical Challenges in the Design and Conduct of Pediatric Clinical Trials

Question 1

There is variability in national definitions of the appropriate risk exposure of children enrolled in research without the possibility of direct therapeutic benefit. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice Guidelines (E-6) use the general term "low" and do not offer any clarifying definition.

- Is an international pediatric-specific guideline needed for conducting research that is without the prospect of direct therapeutic benefit?
- If so, how would creation of this guideline best be achieved?

Question 2

Although some interpretive differences remain, there appears to be general agreement that a proven intervention should not be withheld in favor of a placebo control if doing so would risk serious harm to research participants.

- Is the same standard adequate for randomized controlled studies involving children?
- If not, should the risk standard be as conservative as the standard for enrolling children in nonbeneficial research?
- How would creation of such an international standard best be achieved?

Major Issues

Support for an International Standard for Pediatric Clinical Trials. The consensus was that a global pediatric-specific guideline is needed regarding risk exposure of children enrolled in research without the possibility of direct therapeutic benefit. Having an international standard for pediatric studies will facilitate the more rapid development of pediatric programs without having to consider the thousands of existing guidelines. A universal guideline will result in streamlining the process and will introduce efficiencies.

The Challenges of Establishing an International Standard. Definite challenges are involved in designing an international pediatric study for a particular population using current ethical principles. A number of components must be analyzed before children can be enrolled in clinical trials, including risk level, benefit, and to whom the benefit accrues. Establishing a common standard for risk involves imposing a ceiling on how much risk children can be exposed to without a prospect of direct benefit. Some participants believe that setting a standard for acceptable risk must be balanced against the benefit of the study. Other participants noted that no level of risk is acceptable without benefit to the community.

A better way to frame the issue of an international pediatric guideline might be to state the goal as the efficient conduct of multinational pediatric trials. A great deal of preparatory work must be done first. For example, basic ethical precepts for pediatric research must be laid out that are true across the world. Basic concepts, such as autonomy and justice, must be examined because they are interpreted differently in different countries.

Another challenge regarding the aims of regulation is the need to respond to the vast differences in environments. In some environments, participation in any clinical research is a benefit and 100-percent consent rates are possible. Institutional review boards (IRBs) and investigators must consider the community and package-deal benefit. To develop safe and effective medicines for children, medications must be tested while protecting children from reasonably foreseeable harms and respecting their burgeoning autonomy.

Investigators, ethicists, and regulators should develop some broad principles to be adopted across clinical research undertaken globally. One such principle might be the need for different standards for different age groups. For example, the ability to conceptualize the nature of a study depends on whether a child is 6 months old or 14 years old. Investigators, ethicists, and regulators should consider the possibility of formulating two standards depending on the age of the children involved. Good clinical infrastructure is needed to support a trial, especially in low-income settings. Both intervention and nonintervention groups must be helped with personalized care.

Community Engagement and Informed Consent. Some form of standardization should be in place even though creating such a standard is challenging and difficult. One basic principle is that in determining potential benefit in the process of pediatric research, the child and parent/caregiver must be involved and their views must be engaged. Symmetry between the

partners is needed, the age of the children must be considered, and it should be remembered that people trust people like them, not necessarily doctors, to guide them through ethical minefields. Families want to know that other parent representatives have reviewed the study and were convinced that it should be conducted.

Contextual Risk. The acceptance of risk exists within the community, and the community must decide within certain parameters what level of risk to take. Different communities have different thresholds for acceptable risk. The question is whether it is ethical to conduct research in a country with a high tolerance to risk. The challenges of consent sometimes involve a consenter who is illiterate consenting for an illiterate subject. The focus on children may be wrong. Instead, investigators, ethicists, and regulators should focus on the ability of the person in the trial, irrespective of that person's age, to understand what is happening. If not, an appropriate surrogate must be found.

The question is whether consultation is needed to develop a guideline. If so, who are the people to be consulted and where in the process should this step be conducted—before IRB approval, after IRB approval, during early development of the process? Is the role of the layperson, community representative, or advocate in the IRB to be the funnel for community information that comes to the IRB? Does this step account for delays in the IRB process?

Parental involvement can make clinical trials feasible, possible, and acceptable. Pharmaceutical companies realize that community involvement has a positive effect on recruitment. This involvement should occur at the initiation of the study. It has been demonstrated that involving a parent advocate group enhances the recruitment effort.

Delays in IRB Approval of Clinical Trials. Long delays still exist in implementing clinical research. Regulators fail to realize that the pace of some diseases, such as tuberculosis and HIV, is very rapid in infants and children. Therefore, the absence of any therapy, plus the slow pace of implementation of protocols, can be very damaging to the general population of children and adolescents. The amount of time it takes to conduct some reviews indicates the need for guidance, and highlighting the delays and barriers is the first step forward.

Delays in approval of clinical trials might involve the number of groups needed for approval before a study can start. Centralized IRBs can reduce the number of hurdles without undermining the protections and the quality of the review. However, if the issue is the long time between conception of the study and regulation or approval, changing the regulations might not be the answer. Delays in approval of research can be attributed to the fact that some countries' standards specifically involve children in relation to the informed consent process, but few standards address risk–benefit issues in pediatric populations in the approval process. Intercountry variability is probably not a major cause of delay. The use of centralized IRBs versus local IRBs involves trust and the need for better communication and education as an important element of capacity building and overcoming ethical challenges.

Role of Pharmaceutical Companies. The pragmatic methodology for pharmaceutical companies is to choose countries that offer the path of least resistance and expense. The incentives are commercial for pharmaceutical companies. From a regulator's perspective, guidelines might be helpful in forcing pharmaceutical companies to provide a pediatric investigation program.

Definition of Problems To Be Solved. The focus should be on where the problems exist. One problem is the prospect of direct therapeutic benefit. This problem involves the level of specificity that must be defined. Another problem is that some IRBs do not include pediatricians. Another involves the definition of "condition." An additional problem involves the need to study a particular disease in children without a good animal model. In such a case, it is difficult to establish proof of concept and prospect of direct benefit in a preclinical stage. Risk can be calculated in mathematical terms to quantify harms, but there might be other harms that cannot be quantified, for example, the possibility of developing needle phobia after venipuncture.

Summary. Main discussion topics were as follows:

- The importance of engaging the "community" (parents, children, region)
- The ceiling of risk for children without the prospect of direct benefit in a therapeutic trial
- The importance of an international standard but the difficulty in the interpretation and application of standards because of vagueness
- The need for adequate representation of the community in the development of the protocol.

Proposed Action Items/Next Steps

Models for cooperative review need to be used more effectively or used more widely. International standards for conducting pediatric clinical trials should be developed.

Topic 2: Responding to the Needs of the Local Pediatric Population

Question 1

A research agenda can be driven by a number of factors, including building research and/or clinical infrastructure, delivering otherwise unavailable health care, establishing the safety and/or efficacy of products regardless of the intended market, and developing products to address important health needs of the local population. At times, these differing objectives may be in tension.

- How should these different agendas be prioritized when designing and conducting pediatric trials?

Question 2

There is a general agreement that clinical trials should be designed to be responsive to the health needs of the population within which the research is being conducted. For an individual child

who qualifies for enrollment in a clinical trial offering potential direct benefit, that trial would in a limited way address his or her health care needs.

- What elements should be included in a protocol and/or research contract to address the health needs of the pediatric population?
- What role do investigators, ethicists, and regulators have, if any, in addressing this issue?

Major Issues

Defining the Problem To Be Addressed. The question involves what needs to be changed in the system as it currently exists in order to address the issues involved in the questions. The tension between global and local standards should be addressed in the development of pediatric studies.

Prevention of Exploitation of Children. Children should not be used as a means to obtain scientific knowledge for adults. Obtaining benefit from a pediatric pharmacokinetic (PK) study is a problem because it is highly unlikely that a child will benefit directly from one or two doses of a medication. Certain hierarchies in certain countries might not be worthy of trust regarding the exploitation of children. The question involves whose guidance should be sought to prevent exploitation. In addition, individual versus community priorities must be balanced.

Another question involves the licensing of a medication in the country where a study took place. When a drug development study is initiated, especially in a vulnerable population, a provision should be made for an ongoing supply of medicine to be made available in that country. If the drug company refuses, the ethical question becomes more difficult and might involve whether the condition is chronic or acute.

A plan for implementation at the end of a study might be a way to solve the ethical problem involved in pharmaceutical studies in children. To show long-term benefits, such a plan should be presented to the health ministries and regulatory authorities at the inception of a trial. A particular region or country will have to make the determination regarding the ethics of this situation. It should be noted that medicine development can be stifled because licensing requirements can present a serious disincentive to some sponsors to undertake the study.

In a global network, the issue of sustainability of an intervention becomes more and more possible. However, the idea of benefits to the country versus benefits to the enrolled children raises the question of acceptable versus unacceptable benefits. Another question involves who should decide about acceptable benefits and whether consensus can be reached about that decision-making process. Some countries might accept that the children in a PK study do not have the disease or condition under investigation and will probably never get it, but still allow the study to go on. The FDA's position is that PK studies should be done in a population that is at risk or has the disease. The direct benefit of PK studies in children is the same as the direct benefit of studies in adults. The difficulty is that children are a vulnerable population who are more at risk of being exploited. Exploitation of children and of a population in a region must be prevented.

Another problem involves the predictability of the outcome of research, particularly in early-phase studies. A principle of continuity of care should be established once a study is completed and a benefit is shown for a medicine. This question involves economic issues for the pharmaceutical industry. Another consideration involves whether a community might be coerced into accepting risk that they would not otherwise accept when presented with the possibility of participating in a clinical trial of a drug. Further safeguards are needed to protect against this situation. A sustainability plan must be clearly articulated, and the community must decide whether the plan is in the best interest of its children. Otherwise, concerns will develop involving colonialism or "ethical imperialism."

Risk–Benefit Conflict. A trial might be of benefit to children but not at that moment in time. There might be minimal risk but no benefit except downstream. The question is whether such a trial should be considered unethical. Another ethical quagmire arises from the notion that, for example, a particular community might not consider stunting as a problem. The upshot is that the community must be engaged in making decisions about the clinical study, and the information from the study must be shared with the community.

Collaboration Among All Parties. The role of investigators, ethicists, and regulators must be considered. In a noncontroversial scenario, investigators design a scientifically valid study that has merit. The ethics review committee or regulatory authorities then evaluate whether the study includes appropriate protections. Next, the study is taken to the community. In a controversial scenario, the investigators, ethicists, and regulators might struggle to balance some of the tensions in their roles regarding, for example, coerciveness. Is it appropriate to rely on the community's input to help adjudicate whether the study represents an ethically sound balance of risks and benefits? One participant mentioned the concept of a people's court, which includes a body of like-minded people who grapple with a difficult point and undertake the risk–benefit analysis.

Explicitness, or transparency, is the key to the success of the process. The studies undergo continuous monitoring, and transparency and accessibility are important components of the process. The community should be made aware of a hierarchal list of benefits—to the child, to the population of children with that disease, to the population of children at that age, and so on. Debates should be transparent to the populations involved. Every trial should go through the process of review by investigators, ethicists, and regulators. A practical question is whether the process can be followed expeditiously for all studies. A risk-based analysis might be preferable.

Long-Term Safety, Long-Term Follow-up, and Preclinical Studies. Children are a unique population in that they present a need for safeguards against the possibility of acute medicines resulting in chronic sequelae. Should all children in a study be monitored to treat sequelae? A question arises involving the issue of compensation for harm and the need to follow up children for many years to detect adverse consequences. Guidance can be provided by adequate preclinical modeling, which will be determined by the nature of the medicine. Preclinical modeling can be *in vitro* for special indications.

Summary. Main discussion topics were as follows:

- Prevention of the exploitation of children
- Risk–benefit conflict and the need for a hierarchy to determine benefits (for example, public health, global, or individual)
- Collaboration among all parties
- The possibility of unacceptable benefits to be decided by the community
- Intent to license medication in the country where the study took place
- Issues of long-term safety, preclinical studies for guidance, and long-term followup.

Proposed Action Items/Next Steps

The group did not formally address action items or next steps.

Topic 3: Building International Clinical and Regulatory Capacity

Question 1

The development of adequate clinical research capacity requires both infrastructure (that is, academic framework, facilities, and financial resources) and people (that is, with medical and/or scientific training). There are existing networks that seek to address one or more of these requirements.

- Given the global scope of pediatric clinical trials, should pediatric-specific initiative(s) be developed among national networks?
- If so, what are some of the steps that might be taken to begin such initiative(s)?

Question 2

The development of adequate regulatory capacity requires both infrastructure (that is, academic framework, financial resources, and procedural regulations) and people (that is, scientific, administrative, and legal expertise). There are existing networks and relationships among national regulatory authorities that seek to address one or more of these requirements.

- Given the global scope of pediatric clinical trials, should pediatric-specific initiative(s) be developed among national regulatory authorities?
- If so, what are some of the steps that might be taken to begin such initiative(s)?

Major Issues

Training and Retention of Investigators. Good Clinical Practice, Good Laboratory Practice, and Web-based training programs are very valuable. They facilitate training in developing countries to a great degree and ensure that line workers are trained in a uniform manner. However, deficiencies seem to exist in the training, availability, and preparation of mid-level investigators.

Mid-level investigators typically earn master's degrees, but that step might not be necessary. One solution is to offer short-form training programs, as opposed to graduate studies programs. These short-form programs can be effective in solving the problem of training mid-level investigators. As a contribution to the world community of clinical research, the NIH could make uniform resources available for such training. Another solution is to use the NIH train-the-trainer model in preparation for individual trials. A middle ground between a master's program and a short-form training program might be a minicourse made available through NIH resources to train trainers. That model could be expanded around the globe. Training for administrative or clinical people (for example, secretaries and administrative assistants) in trial sites should include language training.

IRB members need training in research ethics. One participant stated that differences exist in national regulations, but in general they are very similar and do not present obstacles in conducting research studies across countries.

Investigators need training to design successful clinical studies. A strategy should be formulated for training mid-level investigators in designing protocols. A relatively simple training program would be very valuable in all countries. In developing countries, the World Health Organization might be the vehicle for such training programs. Conducting workshops in clinical trials can help to point out mistakes in protocols and result in a helpful dialogue. Likewise, teaching elementary research in hospitals can lead to research projects with a resource point person. Other initiatives can train people for grants management. Certain programs in the United States train clinical investigators in trial design and offer workshops on outcomes measurement focused on particular disease areas.

Is there anything that can be done beyond training to support mid-level investigators? Mentorship programs might be one strategy. Both training and retaining investigators through salary support are important. In addition to salary support, professional and institutionally based rewards include research-protected time, adequate administrative support, and clerical help.

The Problem of Bureaucracy. The culture within the field of pediatrics must be changed to make it research friendly. Bureaucracy is a disincentive to research studies. Investigators carry the added burden of and are responsible for following regulatory policies. One local model provides the infrastructure (nurses, clinical coordinators, and so on), but the clinicians must be willing to do their part as well.

The question involves how the bureaucracy can be streamlined through initiatives that make it easier to conduct pediatric studies. For example, is it possible for a network to provide administrative support to help with the bureaucracy? The organization and training of new employees necessitate introductory, understandable guidance. Bureaucracy training programs are needed to handle regulatory hurdles.

A question is whether any elements of the bureaucracy are unnecessary, for example, the preparation of consent forms, the ethical process, getting consent, and training people in study

design. These are necessary elements of clinical research. Funding sources, whether in industry or government, must appreciate the need for salary support at the clinician level and understand the necessary elements of the bureaucracy that are part of the ramp-up of a study. In capitated studies, how is a person compensated for the required preparation time? Are there any initiatives that could help with improving or removing some of the burdens of the regulatory requirements? If the bureaucracy is necessary, at least it can be streamlined.

The Problem of Recruiting, Enrolling, and Retaining Study Subjects. A major obstacle in doing successful pediatric studies involves recruitment. Investigators often do not consider their job to be recruitment; in fact, they seem to consider recruitment by investigators as unseemly. This situation might be due to the fact that treating physicians and study investigators seem to have competing roles, which might be a reason why investigators hesitate to recruit. Furthermore, some centers see an ethical imperative to separate the two roles to avoid the perception of coercion. The burden often shifts to the investigative team, and skilled coordinators are used for recruitment. If it can be done practically, separating the roles of treating physician and study investigator might be better from an ethical standpoint and to promote recruitment.

Another obstacle in pediatric recruitment is that families are interested in becoming involved, but clinicians must be reminded to raise the issue of research studies when they see their patients. In the United States, it is thought that one of the biggest obstacles to recruitment is a lack of trust in research, particularly among minority groups. But other practical obstacles are more common, such as lack of awareness about the trial, distance from the trial site, and the need for child care. In developing countries, investigators talk to doctors and nurses about clinical trials, and field workers visit sites to tell parents about studies. It has been noted that community coordinators who introduce studies and use the consent form as a training document have a high level of success in recruitment.

A question was raised about the informed consent document itself being a burden. Is its length an issue? Many components of the document, such as drug side effects and daily doses, are helpful. Some of the mandated language, such as that related to health insurance, could be adapted locally to make it more understandable. Use of check boxes is helpful in making the document more attractive. Federal regulations provide a simple form with eight required elements for informed consent and six others to be added as appropriate, but the form has devolved into a 30-page document. In Guatemala, a totally clear, pictorial, nonverbal consent form was created, but it was followed by a 20-page university consent form that was incomprehensible to the illiterate women it was meant for.

Support groups for specific disease areas include networks of parents, Web sites, organizational systems, and annual meetings. These foundations or groups can disseminate information about disease-specific clinical trials in their area and can be very helpful with recruitment by providing patients to doctors involved in the trials and educating the doctors who are involved about their patients. It was emphasized that when parents and patients take an active role in designing trials, recruitment is more successful.

If one of the issues is either recruitment or retention in a research project that is ethically justified, who should have the responsibility of investigating the feasibility of that study being completed? Is it a function of ethics review or is it another regulatory function? Several IRBs want information about recruitment rates to be reported regularly because they are concerned about trials reaching fruition. If recruitment does not proceed at the speed that was originally predicted, IRBs ask investigators to provide an analysis to explain why. Sometimes the requirements of a trial are too onerous—for example, a child must spend a night in a research unit—but such a requirement can be easily modified. This situation again leads to the conclusion that parents should provide input into protocol design. However, it is sometimes difficult to access input from advocacy groups and get needed community feedback. How can the learning curve be shortened so that investigators do not have to face these difficult recruitment issues?

Two-way communication with communities from which subjects will be drawn is necessary in a situation involving an emergency setting without the possibility of informed consent. It is challenging to get people to attend meetings that are randomly scheduled by investigators. It is much easier to obtain this type of participation if the investigators go to already-scheduled meetings in the community, for example, at churches or community centers.

It was suggested that a draft protocol be sent to a coordinator (a nurse or a coordinating staff member) who works in a doctor's office. Such a person can manage the protocol, and that person's feedback, along with family input, can be helpful in advising investigators about practical issues. Coordinators often conduct recruitment, and their value is related to their experience.

In developing countries, vetting the protocol at the community level is key. Parent advisory groups can be valuable partners in a structured network to promote protocols. Community advisory boards (CABs) can be excellent sources of support. CAB members are usually caring and dedicated parents and caregivers of children who are helped by the investigators' knowledge and insight. In CABs, community members review protocols, score them, and give unique insights that are very helpful. In return, CAB members gain camaraderie and mutual support from their service. In general, recruitment depends on constant communication with and feedback from people in the community. In general, interacting with parents forces investigators to reassess study design and commit to flexibility.

Funding and Building Clinical Capacity. In some countries, the capacity to undertake pediatric clinical trials outside oncology and neonatology is limited compared with adult specialties even though pediatricians are very motivated to get better medicines for children. Centralized initiatives for IRB approvals and centralized research and development are government funded in some countries, whereas in the United States, the infrastructure is built on the back of the pharmaceutical industry.

In regard to funding, a fine balance exists among mid-level capacity, job security worries, dependency on grants, lack of ability to predict whether a project will be funded, and retention of

good employees. Each country has its unique complexities. However, an institutional ethos that values research is universal.

Pediatric-Specific Research Networks and Building Regulatory Capacity. A question was raised about the existence of pediatric research networks. European countries have such networks. Can a global pediatric regulatory network for clinical studies be created so that only a single submission is made to a competent authority authorized to act for the network? In the United States, centralized IRBs are becoming more common in industry and NIH-funded studies. Can this development be carried out internationally?

A flexible variety of approaches can be used in cooperative research. Pediatric IRBs can use a centralized approach with representatives from many countries as members. An emphasis on centralized review can overcome some of the local concerns, and institutionally based forms can supplant more commonly used forms. For example, adverse event reporting forms in a Web-based portal can be created in a standardized manner and can be compared across clinical trials involving the same drug.

Proposed Action Items/Next Steps

The group did not formally address action items or next steps.

Participants

Fernando Andrés Rodriguez-Trelles, M.D., Ph.D., Professor of Pharmacology, Universidad Complutense de Madrid, Spanish Medicines Agency, Madrid, Spain
Edward Bartlett, Ph.D., International Human Subject Liaison, Office for Human Research Protections, U.S. Department of Health and Human Services, Rockville, MD, USA
Carl L. Bose, M.D., Professor, Department of Pediatrics, School of Medicine, University of North Carolina at Chapel Hill, University of North Carolina Hospital, Chapel Hill, NC, USA
Mark F. Cotton, M.B.Ch.B., F.C.Paed. (SA), M.Med, D.C.H. (SA), D.T.M.&H., Ph.D., Professor, Pediatrics and Child Health, Tygerberg Academic Hospital, University of Stellenbosch, Tygerberg, South Africa
Sara F. Goldkind, M.D., M.A., Senior Bioethicist, Office of Good Clinical Practice, Office of the Commissioner (OC), FDA, Rockville, MD, USA
Shivaprasad S. Goudar, M.D., M.H.P.E., Professor and Research Coordinator, Women's and Children's Health Research Unit, Jawaharlal Nehru Medical College, Belgaum, Karnataka, India
Bill G. Kapogiannis, M.D., Program Director, Adolescent Trials Network for HIV/AIDS Interventions, Pediatric, Adolescent and Maternal Branch, NICHD, NIH, Bethesda, MD, USA
Steven E. Kern, Ph.D., Associate Professor of Pharmaceutics, Department of Pharmaceutics and Pediatrics, Pediatric Pharmacology Unit, University of Utah, Salt Lake City, UT, USA
Victor F. Larcher, B.A., M.B.B.Chir, M.A., Consultant, General Paediatrics and Ethics, Great Ormond Street Hospital NHS Trust, Great Ormond Street Hospital, London, UK

Boaz Lev, M.D., M.H.A., Associate Director General, Head of the Health Division, Ministry of Health, Jerusalem, Israel

Kenji Matsui, M.D., Ph.D., Project Senior Lecturer, Center for Biomedical Ethics and Law, University of Tokyo Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan

Lynne M. Mofenson, M.D., Chief, Pediatric, Adolescent, and Maternal AIDS Branch, Center for Research on Mothers and Children, NICHD, NIH, Rockville, MD, USA

Dianne Murphy, M.D., Director, Office Pediatric Therapeutics, OC, FDA, Rockville, MD, USA

Jan S. Peterson, M.S., C.C.R.A., R.A.C., Director of Regulatory Affairs, BPCA Data Coordinating Center, The EMMES Corporation, Rockville, MD, USA

Kevin A. Prohaska, D.O., M.P.H., Captain, U.S. Public Health Service Corps, Acting Human Subjects Protections Team Lead, Division of Scientific Investigations, Center for Drug Evaluation and Research, FDA, Silver Spring, MD, USA

Sergio Rego, M.D., M.Sc., D.Sc., Researcher, Department of Social Sciences, Center of Applied Ethics and Bioethics, National School of Public Health/Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

Zhaoxia Ren, M.D., Ph.D., Medical Officer, Obstetric and Pediatric Pharmacology Branch (OPPB), Center for Research for Mothers and Children (CRMC), NICHD, NIH, Bethesda, MD, USA

Rosalind L. Smyth, M.A., M.B.B.S., F.R.C.P.C.H., M.D., F.Med.Sci., Professor, School of Reproductive and Developmental Medicine, Institute of Child Health, University of Liverpool, Alder Hey Children's NHS Foundation Trust, Liverpool, UK

Thomas Soo, M.B.B.S., Deputy Director, Pharmaceuticals and Biologics Branch, Therapeutic Products Division, Health Sciences Authority, Helios, Singapore, Singapore

Perdita Taylor-Zapata, M.D., Pediatric Medical Officer, OPPB, CRMC, NICHD, Bethesda, MD, USA

Dione I. Washington, M.S., Health Specialist, Policy, Training, and Quality Assurance Branch, Office for Policy in Clinical Research Operations, Division of AIDS, National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

David Wendler, Ph.D., Head, Unit on Vulnerable Populations, Department of Bioethics, NIH Clinical Center, NIH, Bethesda, MD, USA

Lutz Wiesner, M.S., Ph.D., Pre-Clinical Section, Division of Scientific Service/Clinical Trials, Federal Institute for Drugs and Medical Devices, Bonn, Germany

Zhimin Yang, M.D., Vice-Chief, Office of Evaluation, Center for Drug Evaluation, State Food and Drug Administration, Beijing, China

Enver Yousuf, B.Sc., M.B.B.S., Chief Medical Officer, Medsafe, Ministry of Health New Zealand, Wellington, New Zealand