Workshop on Ethical and Regulatory Issues in Global Pediatric Trials
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***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

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.

The purpose of the workshop was to examine the challenging ethical and regulatory issues in global pediatric clinical trials. It provided a forum for the mutual exchange of views and discussion among key international stakeholders in the design and conduct of pediatric clinical trials.

Opening Remarks

Robert "Skip" Nelson, M.D., Ph.D., Pediatric Ethicist, OPT, Office of the Commissioner (OC), FDA

Dr. Nelson explained that the fundamental assumption of this workshop is that participants share a commitment to improve access to safe and effective medications for children worldwide. Meeting this goal requires conducting pediatric clinical trials that are scientifically sound and ethically appropriate. Increasingly, these trials are being conducted on a global scale, presenting opportunities and challenges in ensuring that children are adequately protected as researchers seek to achieve the goal of improved access to essential pediatric medications.

This workshop was designed to explore the opportunities and challenges faced in addressing this important need by focusing on three general topics:

- Ethical challenges in the design and conduct of pediatric clinical trials
- Responding to the needs of the local pediatric population
- Building international clinical and regulatory capacity.

The goal for the workshop participants is to identify ways to address these challenges together, whether arising from ethical perspectives, regulatory requirements, or the capacity to design, review, and/or carry out clinical research.

Welcome and Introduction

Murray "Mac" Lumpkin, M.D., M.Sc., Deputy Commissioner for International Programs, Office of International Programs, FDA

Dr. Lumpkin welcomed the participants and noted that while they came from every populated continent, including Asia, Australia, Africa, Europe, South America, and North America, they

were bound by their common deep concern for children. Among the participants were 17 ethicists from 12 countries, 16 pediatric trialists from 9 countries, and 29 regulators from 25 countries. This group was highly qualified to address the ethical and regulatory issues of global pediatric clinical trials to ultimately provide safer and more effective drugs for children.

The workshop was the culmination of the ideas and hard work of Dr. Nelson and Dianne Murphy, M.D. About a year ago, Drs. Nelson and Murphy proposed bringing together ethicists, clinical trialists, and regulators from around the world to discuss ethical and regulatory issues related to pediatric clinical trials, as more and more are implemented each year around the globe. The numbers of pediatric clinical trials have increased due to incentives provided by U.S. legislation over the past 10 years and to incentives provided by European and other countries worldwide. Researchers have declared that they will no longer look at children as "*n* = 1" studies; children are not second-class citizens. The use of pediatric medicines needs to be based on strong, robust science. To determine how to best and most safely use drugs in children, both the strongest science and the toughest ethical guidelines must be applied to protect children. Children should never become commodities in any part of the world as part of the clinical trials paradigm.

Background and Overview: Children's Access to Safe and Effective Drugs and Global Pediatric Clinical Trials

Global Pediatric Therapeutic Trials: Access Based on Data

Dr. Murphy, Director, OPT, OC, FDA

For many drugs used to treat children, there are few data to support safety and efficacy. Surveys in 1973 and 1991 revealed that about 80 percent of listed medication labels disclaimed usage or lacked dosing information for children. Other surveys revealed that only 20–30 percent of drugs approved by the FDA were labeled for pediatric use. In addition, 38 percent of new drugs potentially useful in pediatrics were labeled for children when initially approved.

Drugs studied in adult trials have often been used as treatment for children without adequate data about how the product would be tolerated, if it was effective, or what the safe and effective dose was. The good science that is demanded for adults has not always been demanded for children.

Although children are physiologically and developmentally complex, there are a number of reasons they are not studied. Infancy and childhood are a relatively small part of the lifespan and comprise a smaller population compared with adults, children are generally healthy, and there are many developmental subgroups. Children cannot give consent, which requires family involvement. Assent when appropriate can make this process more challenging. A lack of a long history of product development trials means many endpoints and assessments are not adequately developed to meet regulatory standards. Pediatric trials are technically challenging. Pediatric-specific resources are generally lacking.

Recent European and U.S. legislation has included incentives to conduct pediatric therapeutic studies. Other recent legislation encourages development of pediatric devices. There has been

new focus on translational research. Today, about half of the products used in the pediatric population have had some subset of the pediatric population studied for some indication. More than 325 products now have some pediatric information on the label. Despite this progress, issues remain. Of 330 products that were being developed for children, 57 failed to demonstrate efficacy, usually with no further studies to determine why. Neonates remain mostly unstudied. Device product development now is at least 10 years behind drug development.

International collaboration efforts are improving. Over the past 2 years, the FDA and the European Medicines Agency (EMEA) exchanged product-specific information and discussed a number of general topics. The FDA provided information on 375 Paediatric Investigation Plan (PIP) applications for 324 products, 144 of 324 products were discussed, and 68 of 144 product discussion included participation by FDA review divisions.

The problematic lack of data to properly prescribe therapies for children is being addressed, but major issues remain in the pragmatic and ethical domains. Children must not become a commodity in the effort to earn incentives or to eagerly learn more about how best to use a therapy. Children should only be enrolled in trials that ask a needed scientific question, and the number of children enrolled should be the minimum necessary. There is a collective responsibility of ethicists, clinical trialists, and regulators to ensure the ethical and scientifically sound conduct of pediatric trials.

Pediatric Clinical Trials and the Best Pharmaceuticals for Children Act

Perdita Taylor-Zapata, M.D., Obstetric and Pediatric Pharmacology Branch (OPPB), Center for Research for Mothers and Children (CRMC), NICHD, NIH

The Food and Drug Administration Amendments Act (FDAAA) of 2007 reauthorized several existing laws, including the BPCA 2002, which encourages more studies in children and promotes the development of treatments for children, and the Pediatric Research Equity Act, which continues the FDA's authority to require studies in children concerning certain medical products and under other specific circumstances.

The BPCA 2007 mandates that the NIH is responsible for studies of off-patent drugs. The act allows protection for drugs that have no patent protection or market exclusivity. The NIH is also responsible for developing and publishing a priority list of needs in pediatric therapeutics, including drugs, biologics, or indications that require study. For pediatric studies and research conducted under the revised legislation, the NIH may use contracts, grants, or other appropriate funding mechanisms to award to entities that have the expertise to conduct pediatric clinical trials or other research. The NIH is also responsible for the submission of Proposed Pediatric Study Requests (PPSRs) for consideration by the Commissioner of the FDA for pediatric studies of a drug with an approved application and no patent protection, and for which additional studies are needed to assess safety and effectiveness of the use of the drug in the pediatric population.

Since the implementation of BPCA 2002, many issues were uncovered and many lessons have been learned. There is a pervasive lack of preclinical and phase 1 and phase 2 clinical trial data in drugs that have been used in pediatrics for years, even decades. Extrapolation from adult

studies is not appropriate. BPCA studies have shown the difficulty in predicting dose–response or concentration–response relationships. The nature of some clinical responses in immature individuals is unforeseeable, leading to the possibility of unanticipated adverse reactions. Unique adverse events may occur in children. Pediatric medicines may have effects on growth, development, or health long after the drug's administration. There is a need for innovative designs in safety studies. Ethical and feasibility challenges involving pediatric clinical trials remain, including the use of placebo, sample size, formulations, outcome measures, parental permission, and child assent. Pediatrics lags behind in advances in science and technology, including the development and assessment of biomarkers of disease, characterization of adverse drug reactions, pharmacometrics, and pharmacogenomics. There is limited availability of adequate pediatric formulations.

Among the unresolved issues is the high rate of failed trials. Concern has been recently expressed about the significant number of failed pediatric trials because efficacy could not be demonstrated. According to the FDA, up to 50 percent of pediatric effectiveness trials are not interpretable. Possible reasons that safety and efficacy have not been established include:

- Small sample size
- Endpoints that are not well defined
- Pharmacokinetic (PK)–pharmacodynamic correlations that are not established
- Incorrectly identified dose for efficacy studies
- Feasibility issues
- Ethical constraints in protocol development.

Make Medicines Child Size: The World Health Organization Program on Better Medicines for Children

Anna Ridge, M.B.Ch.B., M.P.H., Technical Officer, Essential Medicines and Pharmaceutical Policies, Medicines Access and Rational Use, World Health Organization (WHO)

According to recent WHO estimates, nearly 10 million children younger than 5 years old die every year. More than half of these deaths are caused by well-known diseases such as pneumonia, diarrheal diseases, HIV/AIDS, and malaria. All of these diseases could be effectively treated with safe, essential child-specific medicines. However, many of the necessary medicines are not currently available in appropriate dosage forms or, if they exist, are not available where they are needed.

The lack of medicines for children is of global concern but is most acutely felt in developing countries due to the high burden of disease in these settings. Recognizing that access to better medicines is a prerequisite for improving health outcomes in children and helping developing countries meet their millennium development goals, the World Health Assembly passed resolution WHA60.20, better known as Better Medicines for Children, in May 2007. The resolution was a call to action for member states and WHO to address the global needs for children's medicines.

Given the increasing importance of improving access to essential medicines for children, WHO and UNICEF joined forces to develop a 5-year program to help address this need. Work

completed so far includes (1) development and publication of an essential medicines list, (2) identification of missing priority medicines for the management of HIV, and (3) PK modeling studies to identify optimum dosing of medicines for common diseases such as tuberculosis and pneumonia.

A formulary is currently being developed, and evidence-based WHO pediatric standard treatment guidelines are being updated. Future work will include promoting access to essential medicines for children in priority countries by promoting their inclusion in national essential medicines lists, treatment guidelines, and procurement schemes and working with regulatory authorities to expedite regulatory assessment of essential medicines for children.

Other key areas that have been identified by the program include the need for further collaboration with regulatory authorities to encourage appropriate drug development and approval processes, developing quality standards for pediatric medicines, advocating for the development of pediatric medicines by the pharmaceutical industry, developing a system for enhancing safety monitoring of medicines in children, and providing guidance on procurement and supply of pediatric medicines.

More research in children is needed, and the research needs to be of a high standard with minimal risk to children. The move toward more quality research in children requires knowledge of what research is being done and where so that duplicate trials are not conducted. To this end, WHO has developed the international clinical trials registry, which will make information about all clinical trials publicly available. A recent update to the registry allows easier identification of clinical trials in children.

Understanding the challenges of undertaking clinical trials in children in resource-poor settings will help inform the development of globally applicable standards and guidelines. The approval procedures at institutional review boards (IRBs) and regulatory authorities may need to be harmonized, and appropriate ethical and regulatory structures will need to be in place. In addition, there must be adequate and appropriate research capacity at the local sites. The role of WHO will be to support ongoing endeavors in these vital areas and provide direction and input where necessary in order to achieve globally applicable standards for clinical trials in children.

WHO is currently involved in a number of activities that will address some of the needs that have been identified in relation to the regulation and licensing of medicines for children. At a WHO meeting in October 2009, academicians and methodologists will meet in Amsterdam to identify ways in which current guidance documents can be adapted to meet the global need and to evaluate the role of clinical trial registration for promoting appropriate research on medicines for children in resource-poor settings. In February 2010, WHO will convene a meeting to initiate the formation of a pediatric medicines regulators network. The network will review the need for developing global regulatory standards.

Children's Access to Safe and Effective Drugs and Global Pediatric Trials: European and International Views

Kalle Hoppu, M.D., Ph.D., Medical Director, Poison Information Centre, Helsinki University Central Hospital, Finland

Success of the various international pediatric initiatives requires a substantial increase in the number of pediatric clinical trials performed, collaboration of all stakeholders including children and their parents, and acceptance by the general public. Intuitively, the general public tends to be reserved on acceptability of pediatric clinical trials. News of violation of ethical principles or disclosures of loopholes in ethical guidelines is likely to seriously threaten success of pediatric initiatives. Over the past several years, several European and international pediatric initiatives have begun.

From 2007 to 2008, WHO—with assistance from the International Pharmaceutical Federation—conducted several training workshops on pharmaceutical development with a specific focus on pediatric formulations. The aims of the workshops were to provide a forum for exchanging and sharing information, knowledge, and good practice in developing, formulating, and manufacturing pediatric medicines.

The Paediatric Regulation entered into force in the European Union (EU) in January 2007. Its objective is to improve the health of children in Europe by (1) facilitating the development and availability of medicines for children aged 0–17 years; (2) ensuring that medicines for use in children are of high quality, ethically researched, and authorized appropriately; and (3) improving the availability of information on the use of medicines for children without subjecting children to unnecessary trials or delaying the authorization of medicines for use in adults. The Paediatric Regulation dramatically changed the regulatory environment for pediatric medicines in Europe.

The Paediatric Regulation provides for the EMEA to develop a European Pediatric Network of existing national and European networks, investigators, and centers with specific expertise in the performance of studies in the pediatric population. The objectives of the European Pediatric Network are to coordinate studies relating to pediatric medicinal products, build up the necessary scientific and administrative competences at the European level, and avoid duplication of studies in children.

Another promising development in pediatric medicines is the International Pediatric Initiative, which will bring together European and U.S. stakeholders, as well as other third countries as appropriate, for the joint development and testing of medicines in children. The initiative will establish a network of Centers of Excellence. Its overall objective is to enhance the availability of medicines for children in Europe and the United States. The initiative is funded through the Seventh Framework Programme of the European Union.

FINPEDMED—the Finnish Investigators Network for Pediatric Medicines—was established in early 2007 as a joint collaboration of Finland's five university hospitals. The network brings together doctors treating pediatric patients, as well as professionals and experts interested in

pediatric trials. So far, the network has received 36 proposals for sponsored international multicenter clinical trials. Unfortunately, most trials offered were of poor quality or poorly planned. Some studies were simply unattractive to investigators. Some had design problems including unethical or unnecessary requirements, bad quality of work by the industry due to low priority given to pediatric trials, and sponsor problems with regulatory authorities' requirements. As part of its harmonization procedures, FINPEDMED has developed (1) trial information and informed consent document templates for clinical trials and (2) graphic picture cards to use as aids when study information is given to young children.

Ethical and Regulatory Issues in Pediatric Trials: The Indian Perspective

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The two organizations that are responsible for regulatory oversight of clinical trials are the Indian Council of Medical Research and the Central Drugs Standard Control Organization, specifically the Drugs Controller General of India. Both organizations have guidelines that encourage research in pediatric populations. The guidelines are, respectively, (1) the Ethical Guidelines for Biomedical Research on Human Participants 2006 and (2) the Drugs and Cosmetics (II Amendment) Rules, 2005, Schedule Y (Requirements and Guidelines for Permission to Import and/or Manufacture New Drugs for Sale or to Undertake Clinical Trials). These guidelines require that ethics committees for reviewing clinical trials protocols include a pediatrician. The guidelines include provisions for assent.

The approval process for all clinical trials involves the following organizations:
- Institutional Ethics Committee
- Ministry of Health of the state for community-based projects
- Health Ministry's Screening Committee, Government of India
- Drugs Controller General of India
- Permission for shipping biological samples out of the country.

Clinical trials conducted by the JNMC are reviewed by the KLE University's regulatory system:
- University Monitoring Committee for Clinical Research and Clinical Trials
- Site Management Office
- Institutional Ethics Committee—constituted per Schedule Y and registered with the Office of Human Research Protections.

The JNMC Women's and Children's Health Research Unit has been part of the NICHD Global Network since 2001. The research unit's primary focus is testing community-based interventions for reducing maternal and infant mortality and morbidity. Its multidisciplinary team's expertise includes obstetrics/gynecology, pediatrics, neonatology, community medicine, and physiology. The team includes information technology support staff. The research unit partners with the District Health System. Its population coverage is about 900,000 people in about 300 villages.

Women's and Children's Health Research Unit's research projects are as follows:

- Maternal and Newborn Health Registry—a population-based registry for tracking adverse pregnancy outcomes in participating communities
- FIRST BREATH—Community-based training in resuscitation for reducing early neonatal mortality
- BRAIN HIT—Home-based, parent-provided, early intervention for promoting child development
- Emergency Obstetric and Newborn Care package for reducing stillbirths, early neonatal mortality, and maternal mortality
- Comparison of two iron doses on zinc absorption from Sprinkles™ as a micronutrient supplement for informing the choice for an interventional trial.

There are a number of challenges to informed consent in pediatric trials in India, including:

- Illiteracy
  - Comprehension of materials
  - Consent recorded with thumbprint
  - Need for witness
- Poverty
  - Need for compensation
- Lack of privacy and confidentiality
- Community "consent"
- Cultural influences
  - Authority vested in elder members of family
  - Health workers trusted and "worshipped"
- Health workers' lack of research experience.

Global Pediatric Trials: The NIH Perspective

Anne Zajicek, M.D., Pharm.D., Acting Branch Chief, OPPB, CRMC, NICHD, NIH

For BPCA 2002, the NIH and the FDA developed a master list of all off-patent drugs that lacked adequate pediatric labeling. In consultation with experts in pediatric practice and research, annual lists of drugs were developed, prioritized, and published. Considerations for prioritization included availability of safety and efficacy data, the need for additional data, the potential to produce health benefits, and the need for reformulation. BPCA 2007 directed the NIH and the FDA to develop, prioritize, and publish annual lists of therapeutic areas and specific needs. In consultation with experts in pediatric practice and research, NIH scientists consider therapeutic gaps, the potential health benefits of research, and the adequacy of necessary infrastructure in developing the annual list. From the priority list, the NIH writes and negotiates a PPSR to the FDA as a draft Written Request (WR). The FDA issues a WR to holders of the New Drug Application (NDA) or abbreviated NDA. If the holder accepts, it conducts the study. If the holder declines, the study is referred to the NIH, which develops requests for contracts, proposals, or grant applications to conduct the study.

Several lessons have been learned from the BPCA Program. First, there have been study design issues involving ethical questions (for example, about risk and use of placebo). There have been

institutional and international differences, specifically, differences among IRBs. In addition, there have been difficulties with determining appropriate outcome measures. Clinical and Translational Science Awards sites have been awarded funding to validate some outcome measures. There has been insufficient infrastructure at the institutional level and with regard to investigators, who are typically trained to conduct academic studies but not develop protocols and oversee entire clinical trials. Finally, there has been insufficient knowledge of regulations by investigators.

In an effort to overcome institutional and international differences, the Department of Health and Human Services Secretary's Advisory Committee on Human Research Protections has been helping to build a communication system for ethics committees and IRBs.

Proposed outcomes for the workshop include:

- A white paper to organize thoughts on the ethical and regulatory issues in global pediatric clinical trials and develop a constructive plan for addressing them
- Collaboration on a PPSR or PIP
- Collaboration on database construction
- Collaboration with international networks, in parallel or in series
- Data sharing
- Funding Opportunity Announcements for research and training, including clinical trial design and bioethics.

Presentation of Background Information for Breakout and Plenary Discussions

Ethical Challenges in the Design and Conduct of Pediatric Clinical Trials

Dr. Nelson

Children are widely considered to be vulnerable persons who, as research participants, are in need of additional (or special) protections beyond those afforded to competent adult persons. The details of these additional protections are not always specified in regulations or guidance. When these additional protections are specified, there appears to be general agreement (perhaps with some exceptions) on the basic ethical and regulatory framework governing pediatric clinical trials:

- Children should only be enrolled in a clinical trial if the scientific objective(s) cannot be met through enrolling subjects who can provide informed consent personally.
- Absent a prospect of direct therapeutic benefit to the children enrolled in a clinical trial, the risks to which those children would be exposed must be low.
- Children should not be placed at a disadvantage by failing to get necessary health care after being enrolled in a clinical trial.

Research Without Direct Benefit (Nontherapeutic). In contrast to the "general agreement," some countries appear not to permit nontherapeutic research involving children. Other regulations appear to discourage nontherapeutic research involving children. Finally, there are regulations that permit nontherapeutic research by using the phrase "direct benefit to the group"

(rather than to the individual) to counter arguments that pediatric research can only be done when there is "direct benefit" for the enrolled children. Even if general agreement is assumed, there are differences in:

- How the level of permissible nontherapeutic risk exposure is categorized
- The terms used to describe the permissible level of risk exposure in nontherapeutic trials
- How these terms are defined, even if the same term is used.

The permissible level of risk exposure for children enrolled in nontherapeutic research may be classified using either one or two risk categories. Many countries appear to use one category of pediatric nontherapeutic risk exposure. Some countries use two categories of pediatric nontherapeutic risk exposure. Regardless of the number of categories, there are several different terms used to describe the permissible level of nontherapeutic risk exposure. Examples include "easily tolerated," "minimal," "minor increase over minimal," "low," "minimal risk and minimal burden," "lower," and "minimal or negligible." In the United States "minimal risk" is defined as "ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." Only one standard (of two) needs to be met to be considered "minimal risk." The definition does not define the reference population (for example, whose life?) In Canada, "minimal risk" is defined as "encountered by the participant in those aspects of his or her everyday life that relate to the research." This definition is similar to the U.S. "daily life" standard but uses "everyday" to qualify "life." The reference population is defined as those persons participating in the research. In Mexico, "minimal risk" is defined as "common procedures in physical examinations or psychological diagnoses or routine treatment." This definition is similar to the U.S. "routine physical or psychological examinations or tests" standard.

The importance of whether a child has a disorder or condition may introduce variability. In the United States, "minimal risk" research does not require that the enrolled child have a disorder or condition, whereas research presenting a "minor increase over minimal risk" does require that the child have a disorder or condition. Many other countries specify that the results of nontherapeutic (and therapeutic) research must be applicable to the children with the disorder or condition who are enrolled in the research.

If pediatric nontherapeutic research is limited to "minimal risk" and "minimal risk" is defined in a way that does not allow a blood test, a single dose PK study in pediatrics of a widely available (and used) nonprescription drug may not be possible. If the United States adopted the Canadian definition of "minimal risk," children who face greater "everyday" risk may be enrolled in "riskier, yet minimal risk" research unrelated to their disorder or condition. Given that the United States has two categories for nontherapeutic risk exposure, and Canada has one, the different definitions of "minimal risk" may result in no practical differences. Canada's varying levels of nontherapeutic risk exposure may mirror the U.S. categories of "minimal risk" (for a child without a disorder or condition) and "minor increase over minimal risk" (for a child with a disorder or condition).

Transition: "Fallacy of the Package Deal." Research protocols may combine "high-risk" nontherapeutic interventions with other interventions that either (1) offer (as a research

intervention) a prospect of direct benefit to the enrolled child or (2) would be considered part of necessary health care for that child. It is possible that such "therapeutic" protocols that contain "high-risk" nontherapeutic interventions are being approved based on the presence of other interventions offering the prospect of direct benefit. However, the evaluation of a research protocol needs to separate "research only" interventions from interventions that offer the prospect of direct benefit. The risks of "research-only" interventions should not be justified by other interventions that offer the prospect of direct benefit. Otherwise one could bundle "high-risk" nontherapeutic interventions with necessary health care in order to justify the nontherapeutic research risk.

Research With the Possibility of Direct Benefit. There is general agreement that children should not be placed at a disadvantage by failing to get necessary health care after being enrolled in a clinical trial. There is also general agreement that research that is not scientifically valid (that is, unable to answer the research question) is unethical. At times, these two principles may be in tension, such as when the scientific choice of a comparator for the control group (for example, placebo, and low ineffective dose) would involve withholding proven effective treatment.

The concept of "equipoise" should be considered. There are two different meanings that should be distinguished: (1) scientific uncertainty and (2) comparable balance of risk and potential benefit. For scientific uncertainty, there must be sufficient uncertainty concerning the answer to the scientific question being addressed by the protocol. With regard to comparable balance of risk and potential benefit, research participants should not be placed at a disadvantage by failing to get necessary health care after being enrolled in a clinical trial. There is debate about the choice of control group in a clinical trial. Some take the position that proven effective treatment should never be withheld in favor of a placebo control regardless of the risk involved. Others take the position that there may be valid scientific reasons for withholding proven effective treatment if there is limited risk exposure.

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Choice of Control Group in Clinical Trials Guideline (ICH E10) and the 2008 Declaration of Helsinki appear to have the same standard for the upper limit of allowable risk exposure from withholding effective or proven treatment. According to the ICH E10, "effective treatment" may be withheld as long as this would not result in "serious harm, such as death or irreversible morbidity." The 2008 Declaration of Helsinki permits a placebo control if it is scientifically "necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm." But there appears to be a subtle difference in emphasis. The Declaration of Helsinki stipulates that one must use "best current proven intervention," whereas the ICH E10 appears more permissive if placebo does not present an unacceptable risk (even if current proven interventions exist).

The 2008 Declaration of Helsinki allows for the limited use of a placebo control. This revision has not been without controversy. For example, the Brazilian National Health Council passed a resolution opposing a prior version of this revision (2000). The draft Canadian guidelines (2008)

appear similar to the revised Declaration of Helsinki: "a placebo control is ethically acceptable… if its use is scientifically and methodologically sound to establish the efficacy or safety of the… intervention [and] it does not compromise the safety or well-being of participants." Other national guidelines appear similar to the ICH E10 standard. Australia considers a placebo control unacceptable if there is "known risk of significant harm in the absence of [effective] treatment."

Questions about the pediatric use of placebo remain. EMEA (2008) discusses the use of placebo controls in pediatrics as follows:

- Pediatric use of a placebo control may be "needed for scientific reasons."
- But use of a placebo in children should be more restrictive than in adults.

The EMEA document suggests that avoiding "irreversible harm" should be the upper limit to allowable risk exposure when using a placebo control in pediatrics. However, this question is not explicitly addressed.

Analysis of pediatric use of placebo should consider the following:

- Placebo administration does not offer a prospect of direct benefit in the context of a clinical trial (setting aside any alleged "placebo effect").
- Risk of placebo product generally is "minimal" (if appropriately chosen).
- Thus, the risk of being randomized to a placebo control group generally is related to the risk of harm from not receiving "proven" or "effective" treatment.

Parental Permission and Child Assent. Parental permission (that is, informed consent) is recognized worldwide as an important protection for children who are being considered for enrollment in a research protocol. However, the feasibility of obtaining parental permission may be a problem in some areas due to great distances, lack of communication infrastructure, social dislocation, high parental mortality, and so on. Absent a parent (that is, a child is an orphan, ward of the state, or living away from home), permission may be obtained from a legally authorized guardian. However, there may be wide variability in how and from whom such permission should be obtained.

Some jurisdictions allow for older children and/or adolescents (that is, minors) to consent to research participation under limited circumstances, such as when the intervention or procedure is one to which minors can consent under the laws of the local jurisdiction. The laws (and the interpretation of these laws) allowing for a minor to consent to research without parental permission vary widely. There is variability in the age and maturity at which child assent is to be obtained, and there is variability in whether and when a child's dissent should be respected. Local laws, community values, and customs play an important role in seeking solutions to approaches to parental permission and child assent/dissent

Questions for Discussion.

- With regard to research not offering direct benefit (nontherapeutic):
  - Is there a need for an international pediatric-specific guideline for conducting research that is without the prospect of direct therapeutic benefit?
  - If so, how would creation of this guideline best be achieved?

- With regard to research offering possibility of direct benefit:
  - Is this 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?

Responding to the Needs of the Local Pediatric Population

Rohan Hazra, M.D., Medical Officer, Pediatric, Adolescent, and Maternal AIDS Branch, NICHD, NIH

The commitment to improving the access of children worldwide to safe and effective medications requires conducting pediatric clinical trials that are scientifically sound and ethically appropriate. Clinical research should be responsive to the health needs and priorities of the communities in which it is conducted. Therefore, international investigators and their teams should be deeply involved in protocol development early in the process. Global health research—particularly pediatric clinical trials—needs to be conducted through partnerships, and there should be an ongoing dialogue among the partnering countries. Partners need to be aware of, committed to, and respectful of host community values, needs, norms, and social practices. Partnerships should promote clinical research that is both valuable and designed to answer questions deemed important by those involved and should engage in negotiation about benefits openly determined to be fair.

There are many challenges to responding to the needs of the local pediatric population:

- Limited numbers of patients (potential participants)
- Need for large numbers of sites
- Profound anatomical, physiological, and developmental differences based on age
- Pediatric work force that is stretched thin
- Participation in large multisite trials not rewarded for academic promotion
- Lack of drug formulations appropriate for infants and children
- Multiple and, at times, contradictory requirements (for example, from IRBs, national and other governmental bodies, regulatory agencies, and study drug importation)
- Attempts to maximize efficiency by trying to answer multiple questions, which increases the complexity of the study and the development time
- Inadequate planning for sufficient study personnel
- Rapid personnel turnover/job security
- Difficulty in attracting subjects to the study site
- Extreme poverty, substance use, and substance abuse
- Vast geographic distribution and mobility of study populations
- Civil unrest
- Lack of integration and coordination among health systems and researchers
- Need for clinical trials insurance
- Difficulty in measuring adherence to protocol
- Varied rules and regulations regarding repository specimens
- Critical need to evaluate long-term safety and efficacy, which is difficult and expensive
- Slow development, implementation, and enrollment, rendering original questions obsolete.

Responding to the Needs of the Pediatric Population: The South African Perspective

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About 3 billion people—one-third of the world's population—are between the ages of 0 and 24 years. This age group comprises more than half of Africa's population and about half of South Africa's 48 million people. More than 20 million South Africans are younger than 18 years. South Africa has the largest HIV epidemic in the world and is the epicenter for tuberculosis. The highest disease burden in South Africa is due to communicable diseases.

Although South Africa provides an opportunity to conduct internationally favorable research in both communicable and noncommunicable diseases, there are a number of logistical considerations for implementing trials in minors. For example, South Africa's people have diverse origins, cultures, languages, and religions. Because South Africa has areas of affluence and areas of grinding poverty, there are disparities in health care services and socioeconomic status. Benchmarks for ethical clinical research in developing countries must include:

- Collaborative partnership
- Enhanced social value
- Scientific validity
- Fair selection of study population
- Favorable risk–benefit ratio
- Informed consent
- Respect for study participants
- Independent review and public accountability.

As part of a clinical trials feasibility study, the Pediatric AIDS Clinical Trials Group (PACTG) interviewed 200 South African stakeholders in discussion groups. Stakeholder responses were used to develop a working model for pediatric clinical research. The first components of the model involve the parent/guardian and the minor and issues of informed consent, parental consent, and confidentiality. Trial compensation and reimbursement are other issues.

The next components involve the pediatric community, youth and other community advisory boards, and the community at large. Issues are who benefits from the research and when the benefits are received, both during the research and when the research is completed.

The research environment is another component. Depending on the type of research, the environment should be youth/child friendly, have adequate expertise, be free/accessible, ensure that standards of care/prevention are met, ensure adequate referral for ancillary services, and consider plans for sustainability.

As all the components are considered, the working model becomes more complex with competing priorities. Every pediatric clinical trial should be considered a long-term project. The

research should ensure community education, consultation, investment, "buy in," and participation. When research is working well, there is collaboration among the sponsor, ethicists, regulators, the community, services, and the local research team.

Capacity Building for Health Research: Examples from the Division of AIDS

Liza Dawson, Ph.D., Branch Chief, Division of AIDS (DAIDS), Human Subjects Protection Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH

The DAIDS is one of four research divisions at the NIAID. Its research portfolio includes six clinical research networks:

- AIDS Clinical Trials Group
- International Maternal, Pediatric, and Adolescent AIDS Clinical Trials (IMPAACT)
- HIV Prevention Trials Network
- HIV Vaccine Trials Network
- Microbicide Trials Network
- International Network for Strategic Initiatives in Global HIV Trials (INSIGHT).

The DAIDS research portfolio now includes about 70 international sites, not including sites affiliated with the INSIGHT network. The rationale for choice of countries/sites follows science, clinical need, and collaborative relationships. There is a rigorous DAIDS site approval process. There is often substantial capacity building at DAIDS sites, including laboratory infrastructure, staff training, pharmacy, equipment, and so on.

The DAIDS research is responsive to the needs of local populations. Two examples are:

- A5207—a study of three different drug regimens to prevent drug resistance in women who receive nevirapine to prevent transmission of HIV to their infants
- P1060—a study of treatment regimens for infants who become HIV infected despite receiving single-dose nevirapine for preventing mother-to-child transmission.

General concerns about capacity building include sustainability, funding and host country buy-in, limits on NIH authorization for use of funds for nonresearch costs, and the need for interface and integration of clinical research capacity with health system capacity for clinical care. Challenges to capacity building include:

- Need for experienced clinical investigators and study staff
- Research site capacity and infrastructure
- Ethics committees' review
- National regulatory authorities.

Building host country research capacity is not only pragmatic, but also ethically necessary. Host country researchers' unique perspectives and ownership of research are critical. Long-term partnerships and true collaboration are necessary processes. In addition, capacity building promotes opportunities for more equal partnerships between external and host country researchers and organizations.

Research in developing countries, addressing local and regional health priorities, is essential to advance health care and health systems to meet current challenges. Research funded by the DAIDS is highly relevant to the needs of the populations being studied in clinical trials. However, the implementation of research protocols at some international sites can face major logistical and regulatory challenges. Capacity building for clinical research and for ethical and regulatory oversight is necessary to accomplish these goals. True partnerships between external sponsors, funding agencies, in-country researchers, and national authorities are needed. Trust, shared decision-making, and communication are essential.

Building International Regulatory Capacity

Agnès Saint Raymond, M.D., Head of Sector, Paediatric Medicinal Products, Scientific Advice and Orphan Drugs (SAOD) Sector, EMEA

There are a variety of regulatory activities related to pediatric clinical trials:

- Manufacturing authorizations (for example, complying with Good Manufacturing Practices)
- Regulatory authorization of clinical trials, which cover scientific and ethical issues
- Ethics committee/IRB review and approval
- Requirements for approval dossier
- Evaluation of medicines for approval (quality, safety and efficacy, and product information)
- Inspections
- Pharmacovigilance, monitoring of safety.

The need to build regulatory capacity is more acute in developing countries where resources, expertise, and priorities do not allow full assessments of medicines for adults and permit even less assessment for children's medicines. Pediatric formulations assessment is a major issue. The current practice in many developing countries is simply "acceptance" of other countries' regulatory assessments (for example, by the FDA and EMEA). This approach does not recognize priorities, region/country specificities, or decision power.

The need for ethics committee/IRB review and approval is clear for all countries. However, there is often lack of training in pediatrics, lack of resources (financial, infrastructure), and lack of expertise or volunteers. There is a need for accumulating and exchanging knowledge in order to build international regulatory capacity.

An example of multinational collaboration of regulatory authorities is the European System for approval, which includes up to 30 countries. Over 20 years, the system has evolved from parallel independent evaluations to a single, unique framework. The framework is a based on trust, mutual recognition, and identical standards.

Regulatory authorities can collaborate in networks (for example, in Australia and New Zealand), but there are requirements for identical or very similar legal frameworks. There must be a willingness to participate, and there must be mutual trust. The added value among collaborators needs to be recognized.

Pediatric-specific initiatives should be developed among national regulatory authorities, especially for capacity to conduct and assess pediatric research (for example, pediatric pharmacology and pediatric formulations) and certainly for ethics committee/IRB reviews and approvals. There needs to be agreement of common standards, where relevant. Initial steps for pediatric-specific initiatives are:

- Find the added value for regulatory authorities and agree on priorities
- Set up a participative (not patronizing) system
- Agree on programs and program content
- Agree on teaching environments, both theoretical and practical
- Monitor impact and reward success.

Breakout Sessions

Four breakout groups met separately to discuss three topics, address related issues, and answer two corresponding questions for each topic. Their discussions in response to the questions were compiled and summarized in three presentations.

Breakout Session Summary Presentations

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

Rapporteur: Francis Crawley, Executive Director, Good Clinical Practice Alliance–Europe, Brussels, Belgium

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 ICH Good Clinical Practice Guidelines (E6) 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 1 Discussion. The following summarizes the breakout groups' discussions in response to question 1:

- Assessments of permissible risk exposure are context-dependent (that is, situational) and depend on many factors, including culture, severity of the condition, and the epidemiology and natural history of the disease. For example, a simple blood test may, in some contexts, be perceived as "high risk."
- Support for a "sliding scale" of permissible risk (that is, "risk is relative") was tempered by the recognition of a need for a "ceiling" of permissible risk for nontherapeutic trials. This "ceiling" was not specified, but its purpose would be to protect against a community accepting excessive risk out of perceived "vulnerability" to, for example, the disease under study.
- One group felt that "minimal risk" should be defined by an "ordinary medical encounter" and not "daily life" given the wide range of variability between communities.

- In general, there was support for the development of an international standard for the additional protections for children. However:
  - It may be difficult to strike a balance between "too vague" (that is, not useful) and "too specific" (such that needed flexibility in light of local variability would be inhibited).
  - There is a risk of oversimplification.
  - There is a need to set such development in the context of basic principles such as autonomy and justice as a way to reframe the discussion.
  - Any forum for the discussion of these issues on a global scale needs to be inclusive of all "voices" (and not only industry/regulators from developed countries).
- One group supported the need for community engagement in these issues, with a need for real partnership and seamless, transparent processes by which this partnership would be structured. This suggestion seeks to address the asymmetry between partners and incorporate in some way the views of parents and children.

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?

Question 2 Discussion. The following summarizes the breakout groups' discussions in response to question 2:
- Overall, there is a diversity of opinion on the use of placebo in pediatric clinical trials (and a reported diversity of national approaches).
  - Some groups felt that the prohibition against the use of a placebo, in general, was too restrictive and may inhibit scientifically valid and efficient pediatric trial designs.
  - The acceptable risk when using a placebo should be lower than in adults, but no group specified what this level of pediatric risk exposure would be.
  - Others were more protective, believing that available "effective" treatment should always be used.
- "Standard of care" should be considered, but there was diversity of opinion on the evidence required for such a standard to be considered an adequate control. Considerations included the length of clinical use and whether (the extent to which) one could consider data from adults in support of efficacy.
- Different sources of resistance to the use of placebo controls were identified, ranging from ethics committees to regulatory agencies and parent groups. Enrollment in placebo-controlled trials may be difficult.

General Discussion. In the breakout groups' discussion of both questions, there was a desire for more data on the nature and extent of any "practical" problems arising from these issues.
- What are the differences between adult and pediatric studies in this regard?
- Do the differences in language and possible interpretation lead to real differences in protocol design, approval, conduct, and review?

- Further discussion would be enhanced by using real examples.
- One group speculated that there is likely more variability in the assessment of protocols within a country (using one approach) than there may be across countries (using different approaches).
- In moving toward possible solutions, there is a need to better define the problems to be solved.

A couple of groups briefly discussed the requirement for children enrolled in a clinical trial to have a disorder or condition. Enrolling children with a disease who are currently asymptomatic was not seen as problematic. The groups discussed the definition of a "condition" and what it means to be "at risk." One group discussed some of the issues in parental permission and child assent as important practical problems in conducting clinical trials. Special note was made about the needs of adolescents.

Response to Topic 1 Summary Presentation. In a general discussion of the topic 1 summary presentation, the meeting participants identified the following issues:
- Context-dependent risk assessment
- Definition of best available treatment
- Local care standards versus a world care standard
- Trial design and rationale for the use of placebo control
- Need for standards and definitions of low risk and minimal risk.

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

Rapporteur: Steven Kern, Ph.D., Associate Professor of Pharmaceutics, Department of Pharmaceutics and Pediatrics, Pediatric Pharmacology Unit, University of Utah

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 clinical trials?

Question 1 Discussion. The following summarizes the breakout groups' discussions in response to question 1:
- There appeared to be agreement that a pediatric clinical trial ought to benefit the population of the "host" country and that exploitation (that is, conducting a clinical trial in one location simply for benefits to be accrued elsewhere) is unethical.
- Some groups expressed the view that individual benefit from enrolling in the clinical trial, including the limited provision of posttrial access for the enrolled (but not general) population, was insufficient.
- The benefit to the population does not take priority over the evaluation of the appropriate risk versus potential benefit for those individuals to be enrolled in the clinical trial (especially

children). Children being placed at risk merely for the good of the community is ethically problematic.

- There appeared to be agreement that a pediatric clinical trial protocol needs to be evaluated on its own merits (that is, risk versus potential benefit) and not as part of an overall development package (that is, added infrastructure). Product development should come "first," and infrastructure should "come along for the ride."
- One group identified a hierarchy of "benefits" and listed the order of ethical priority as (1) individual, (2) population, and (3) global.
- The local evaluation of how the clinical trial fits into national health priorities can be complex and may involve the development of infrastructure using a clinical trial that is not directly targeting a national health priority. Population benefits may include needed laboratory devices, facilities, training, knowledge transfer, and so on.
- Currently there are no legal or regulatory structures to enforce agreements for posttrial access.
  - There is a risk that such structures would inhibit pediatric research.
  - Even though a regulatory agency may require submission of data, it cannot require that the product be marketed.
- There was concern expressed that there should be an international consensus on the importance of a sustained commitment to improving the health of the population.
  - Otherwise, clinical trials would flow to the most permissive country.
  - There would need to be some flexibility in requesting this commitment because some sponsors may not be able to afford much (for example, a small start-up funded by a nongovernmental organization).

Question 2. There is 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, or regulators have, if any, in addressing this issue?

Question 2 Discussion. In response to question 2, the breakout groups developed a "wish list":

- Long-term follow-up (especially safety), which is challenging
- Standards of pediatric expertise
- Posttrial access
- Research-related injury
- Community engagement, especially protocol development (includes parents and site staff)
- Reporting back to the community
- Provision of necessary health care using an appropriate standard (caution: strong inducement; solution: community involvement)
- Contracts may vary between sites, depending on local needs
- Sustainability plan
- Effective and efficient use of data generated by the clinical trial.

General Discussion. A general theme throughout the discussion of these two questions, but especially the first, was the need for transparency throughout the process. There needs to be a compelling justification for the use of a given population in a clinical trial, with due consideration given to the questions of individual and population benefit. It would be helpful to have data about the extent of any problems in this area. A start would be to look at the location of pediatric clinical trials and determine whether data from the trials was submitted for registration in that location. However, the use of existing databases (for example, the WHO international clinical trials registry, EudraCT, and ClinicalTrials.gov) may be currently limited, given inaccuracies in the data and the time lag between posting of the clinical trial listing and the eventual submission of data to national regulatory agencies.

Response to Topic 2 Summary Presentation. In a general discussion of the topic 2 summary presentation, the meeting participants identified the following issues:

- Ethical "drift" of benefits to nonstudy populations, communities, regions, or country, without risks to or exploitation of the pediatric study population
- Clarification of the term "ethically sound"
- Hierarchy of benefits: (1) child, (2) family, (3) population, (4) community, and (5) country
- Time between clinical trial and evidence of benefits
- Vulnerability of study populations and countries to exploitation.

Topic 3: Building International Clinical and Regulatory Capacity

Rapporteur: Hidefumi Nakamura, M.D., Ph.D., Director, Division of Clinical Research, National Center for Child Health and Development, Tokyo, Japan

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 1 Discussion. The breakout groups identified the following steps for beginning pediatric-specific initiatives:

- Training
  - Investigators and other individuals (for example, site staff, IRB members, clinical pharmacologists, mentors, and experts in Good Clinical Practice [GCP]/Good Laboratory Practice)
  - Strong support for GCP as an "appropriate standard"
  - Methods: mini-courses, "train the trainer," and academic programs
  - Community education to foster greater involvement
- Retention
  - Need to "change the culture" (for example, add research-protected time, adequate administrative support for completion of necessary paperwork, and promotion for clinical trial participation)

  - Adequacy and security of funding (can one "plan ahead"?)
- Recruitment and enrollment
  - Adequate ancillary staff, community engagement (is there a role for IRBs?)
- Discussion of the need for "pediatric-specific networks" that are not simply disease-based (although disease-based networks are important)
  - Sustainability and funding (academic versus industry)
  - What is the "added value" of the network to those already doing clinical trials?
- Sharing of experience
  - Project: share best practices in establishing different network models
  - Clinical trial research tools, data sharing, expertise, and information sharing
- Possible demonstration project (IMPAACT)
  - Tracking a current trial in development through the process to identify areas in need of better coordination and harmonization.

Question 2. The development of adequate regulatory capacity requires both infrastructure (legislative frameworks, financial resources, and procedural regulations) and people (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)?

Question 2 Discussion. The following summarizes the breakout groups' discussions in response to question 2:

- Build on existing bilateral and multilateral relationships
  - Memorandum of understanding
  - Confidentiality agreements (overall or protocol-specific)
  - Regional and global networking
  - Sharing of expertise and work sharing between agencies
- Build "regulatory science"
  - Share expertise in important areas of pediatric product development (for example, pharmacogenomics, PK modeling, endpoints, and trial design)
- Develop mechanisms
  - Use of existing (and developing) international platforms (for example, the WHO International Conference of Drug Regulatory Authorities [ICDRA] program**)**
  - Use of communication technology.

General Discussion. The breakout groups provided cautionary notes:

- The development of research capacity can drain resources away from needed health care capacity, especially in underserved areas where health care workers may be poorly compensated.
- Capacity building in research and health care needs to be integrated and coordinated.

Response to Topic 3 Summary Presentation. In a general discussion of the topic 3 summary presentation, the meeting participants identified the following issues:

- Publication of study results; obligation to make results public
- Types of networks: disease-specific, non-disease-specific, women–children
- Need for mechanisms to bring clinical trialists/researchers together
- Need to train mid-level young investigators
- Need for curricula in clinical study design (not a master's program)
- Training for IRBs
- Timing of access to/availability of study data
- Need to establish communication mechanisms
- Quality improvement/quality assurance of research processes
- Improving the effectiveness of research
- Parents' and pediatricians' awareness of the lack of safety and efficacy data for commonly used pediatric medicines.

Plenary Discussion

Moderator: Dr. Nelson, M.D., Ph.D.

Topic 1—Ethical Challenges in the Design and Conduct of Pediatric Clinical Trials. Discussion topics were as follows:

- There is a need for information on status and activities of global pediatric clinical trials. Information would include differences in the way protocols are handled. Ways to post such information should be explored.
- Information technology (for example, the Internet/a Web site) should be leveraged to provide examples of clinical trials from different areas of the world that are in the public domain. Descriptions of the clinical trials would be posted to allow for open comment and evaluation. An open, interactive format would facilitate dialogue on the ethical views of those particular trials. This would provide a case-based approach to analyzing protocols from different perspectives. The Web site would include a range of trial types and designs and could include publicly available trials that have been reviewed by the Federal 407 Panel. Innovative designs for pediatric clinical trials would be included.
- Issues such as ethics, extrapolation, neonates, and endpoints should be examined to determine the differences in the ways regulatory agencies handle clinical trials.
- There is a need to develop core competencies of ethics review committees. Regulatory-accountable training should be considered.

Topic 2—Responding to the Needs of the Local Pediatric Population. Discussion topics were as follows:

- There was a general consensus among meeting participants that clinical trials of local populations in host countries should benefit those local populations. Posttrial benefits such as access to approved drugs can be negotiated through contracts. Currently there are no mechanisms or international regulatory organizations that can enforce these types of agreements.
- There should be agreement among countries to adopt principles that say there must be posttrial benefits. If sites are competing, there should not be a "race to the bottom."
- In addition to putting requirements in guidelines, bargaining positions of the host countries could be strengthened through the exchange of information about agreements regarding

benefits and posttrial drug access. Web sites could be developed that would describe the types of benefits that developing countries have negotiated with sponsors. The Harvard School of Public Health will post this type of information on its Web site (www.hsph.harvard.edu/research/bioethics).

- NIH has a guideline regarding posttrial access to antiretroviral drugs. The guideline affects treatment trials funded through NIH. The guideline states that investigators should identify sources on antiretroviral treatment for people who are in the trials and need to continue treatment.
- There are ethical issues on the population level concerning indirect benefits (for example, study participants may not benefit from the research but children in the future may). Such information should be disclosed in advance of trial implementation (for example, there could be a disclaimer in the informed consent).
- There is a need to share information about what is happening during a trial (for example, standards of care); investigators need to know what to advocate for.
- Trial registries could include questions about what provisions have been made to address local needs and provide benefits during and after clinical trials. Ethical issues (for example, local needs, benefits, and standards of care) should be specifically addressed in the standard form for submitting protocols. The European Union Drug Regulatory Agency (EUDRA) reports when an ethics committee has not approved a trial application for ethical reasons. This information is reported when protocols are published.
  Action item: Regulatory agencies should explore how to achieve the introduction of elements to ensure that these issues are addressed in protocols either within the protocol registration process or within the protocol process through EUDRA or ICH.
- Mechanisms could be developed to modify the clinical trials registration process to include specific elements addressing ethical issues such as standards of care, local needs, and benefits.
- Local populations should be involved in identifying the types of posttrial benefits they want, which may not necessarily be what others think they need.
- A mechanism is needed to track trial data that are obtained in one location, but the drug is not submitted for registration in that location. Regulatory agencies should address requirements for submission of registration. For example, in Europe, a drug must be submitted for registration within 6 months of trial completion.

Topic 3—Building International Clinical and Regulatory Capacity. The following topics regarding regulatory capacity were discussed:

- The existing ICDRA mechanism could be leveraged to facilitate ongoing dialogue about regulatory capacity building.
- Although labor-intensive and costly, scientific expertise can be shared by identifying regulatory needs and putting experts on site to provide the expertise. If drug companies do not submit in those countries, there is no need to evaluate applications and build capacity. Drug regulation policies should be harmonized across nations, but a mechanism needs to be developed.
- Experiences and information should be shared with developing countries in an effort to build capacity to a level that might enable these countries to more effectively work within the global community to benefit from initiatives in the United States and European Union. For

example, ICH members could reach out to nonmembers and share their experiences and information.

The discussion topics regarding investigator capacity were as follows:

- Remote training through Web-based short courses
- Using requests for information (RFIs) to identify elements of a research training program
- Identifying and overcoming challenges to conducting research in clinical practices
- Training for hospital- or institution-based practitioners to become involved in clinical trials
- Educating pediatricians about labeling
- Using current Web-based technologies (for example, such as that used by Internet social network sites) to develop a forum for exchanging information among investigators
- Sharing best practices in different network models
- Tracking clinical trials from concept stage to identify bottlenecks in an effort to enhance coordination and harmonization
- Investing in development of non-disease-specific pediatric network infrastructure (for example, the Medicines for Children Research Network in the United Kingdom)
- Raising awareness among funding agencies that clinical trials are long term, generally longer than 3 years
- Monitoring status of clinical research centers after trials are completed.

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