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 B 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 (ICH) 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?

Major Issues

Background. There are concerns that differences (that is, "mismatches") among national and international pediatric research guidelines may be inhibiting the ability to conduct pediatric clinical trials. There is a lack of clarity and agreement of the definition of "low risk" among guidelines, which may also be inhibiting pediatric clinical trials. There are differences in the amount of risk that children are allowed to assume to be in a control group. The breakout group was asked: Are children allowed to be in a placebo control group, and, if so, under what circumstances?

Definition of Risk. There is debate within the United States about whether any nontherapeutic studies—regardless of risk—should be allowed for children at all. There is no clear rationale for why nontherapeutic studies are allowed. Nontherapeutic research on adults is not allowed without informed consent. Because a child cannot consent, nontherapeutic research in children should not be allowed at all. That parents can authorize research for their children has no parallel in the adult world. Historically, the exception for low or minimal risk has been too flexible. There have been recent discussions about nontherapeutic brain biopsies in children with brainstem gliomas. Although there may be a scientific rationale for such biopsies (for example, learning more about the disease and developing therapies), the procedure has considerable risk. Yet, some investigators believe the scientific merit is great enough to warrant this type of nontherapeutic research. And indeed, this research is being pursued.

There are no specific regulations in the United States about research on mentally ill adults. There are several amendments to the regulatory rules for children, prisoners, and fetuses, but none for mentally ill or mentally incapacitated adults.

Among different U.S. institutional review boards (IRBs) there are differences in interpreting whether research is low or minimal risk. The problem is that the language is not understandable, and the continuum of nontherapeutic to therapeutic research is not recognized.

The definition of risk needs to be clarified. Interpretations of risk may depend on the definition and on the makeup of the IRB. The differences in IRBs may trump any international differences in the definitions of risk. South Africa's guidelines adhere to the U.S. guidelines' definition risk. In Australia, the IRB decides what is reasonable, but ultimately it depends on what parents decide is reasonable. The parents' decision may be based on community acceptability/standards. The IRBs may decide what types of risk are presented to the parents.

Therapeutic Versus Nontherapeutic. There is a division between "therapeutic" and "nontherapeutic," and modern concepts/definitions for these two terms need to be developed. Nontherapeutic research may eventually result in therapeutic uses (for example, neonatal diabetes screening). A complicating example of nontherapeutic research is the fact that most clinical trials fail. Most of the drugs fail in early phase studies because of safety or efficacy reasons.

Clinical, therapeutic research is conducted for the same reason that nontherapeutic research is conducted: to advance scientific knowledge. The interests of patients/subjects are always secondary to the interests of the clinical trial. Because of this, there may be a rationale to stop using the phrase "research with a reasonable prospect of therapeutic benefit." A better phrase is "research with a reasonable prospect of direct medical benefit."

A distinction should be made between interventional and noninterventional studies.

Contextual Ethics. There needs to be a new concept/definition for this term.

Risk–Benefit Ratio. All research is experimental. The risks and the benefits of research should be identified. Benefits can be broadly defined in terms of whole communities or individuals. Once defined, benefits can be weighed against risks.

International Variation of Allowed Procedures. An international survey on the use of sedation or anesthesia in pediatric research revealed wide variation across countries and even within departments. Some institutions have approved the use of anesthesia in nontherapeutic studies.

Age of Consent. In Spain, there is a higher standard of consent for clinical research than for medical treatment. A person can consent to medical treatment at 16 years of age but cannot consent to clinical research until 18 years of age. The legal basis for this difference is related to the higher perceived risk of research versus normal therapy.

Spectrum of Risk. A range of acceptability/risk of different procedures (for example, venipuncture to brain biopsy) could be developed. The conditions under which each procedure is acceptable or unacceptable due to risk could be defined. There could be standards on why people agree on acceptability/risk. Procedures could be viewed in terms of burden or discomfort. Although there may be minimal risk of, for example, an unnecessary venipuncture, such a procedure may be unacceptable, particularly to the child. The reasons why one nontherapeutic procedure is acceptable and another is not may depend on how the risk is explained.

In international settings, there are important cultural components. There are differences in the interpretation of risk in different international settings. In some Asian countries, blood draws from infants are not acceptable because they are perceived as being more than minimal risk. Education is often needed to explain that taking blood does no harm and to raise awareness about the role of nontherapeutic procedures in pediatric clinical research.

A procedure may have different levels of risk depending on where the procedure is performed. For example, venipuncture performed in home may have a greater chance of infection—and therefore greater risk—than venipuncture performed in a clinic or hospital.

There may be different standards of risk for healthy children compared with children with a disease or condition. More nontherapeutic research may be allowed on a child with a disease or condition (for example, cancer) than on a healthy child.

Assumption of Pediatric Research. There is a pervasive assumption that it is unethical to conduct any pediatric clinical research, even if it involves minimal risk. The ethics behind this assumption may need to be challenged.

Summary. There is continuum of risk that involves not just the procedure and not just a particular child or the child's history. Perceptions and interpretations of risk involve cultural contexts and the context in which the research is conducted. There may need to be a more complex description of what risk ought to be than anything regulations currently capture. The

contextual framework of risk includes cultural issues, epidemiology, and natural history. Risks in any context must be weighed in terms of potential benefit.

Proposed Action Items/Next Steps

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

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

Placebo-Controlled Trials. A placebo-controlled trial may be acceptable if it involves a serious or life-threatening condition for which there is no effective treatment available. There is controversy, however, if there is an effective treatment but it is not locally available. If research on a particular drug is conducted in an area where the drug is not available, there is a 50-percent chance that a child will receive an effective drug. If the research is not conducted at all in the area, there is a 0-percent chance that a child will receive an effective drug. The critical issue is whether a clinically proven but not locally available drug is sufficient justification for conducting a placebo-controlled trial.

Standards of Care. Standards of care should be considered in the context in which placebo-controlled trials are conducted.

Benefit. Children who receive placebo in clinical trials may potentially benefit from increased monitoring. Benefits may not always be strictly medical benefits.

Extrapolation. Extrapolation of a drug's efficacy in children based on its efficacy in adults may not be reliable. A child receiving a drug with purported but unproven efficacy in a placebo-controlled trial may have a higher risk of adverse events (for example, cough and cold medicines). If, based on extrapolation, a drug's efficacy is assumed, it is not acceptable to use a placebo. If the drug is not more efficacious than placebo, it is acceptable. Drugs that are considered safe and effective in adults may not be safe and effective in children when used off-label.

Vaccines. Vaccine trials should be differentiated from therapeutic and nontherapeutic trials.

Summary. The group generally agreed that placebo-controlled trials can be conducted under certain situations and for various scientific reasons. One issue is that a drug may not be effective in children. There may be a reasonable prospect of benefit to individuals, but given the high rate of trials that fail, receiving a placebo may not be any worse than medicine that is not beneficial and may have risk of adverse events.

Proposed Action Items/Next Steps

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

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?

Major Issues

Health Care Improvement. Clinical trials can serve as catalysts to improve general health care by bringing in doctors, medicines, and equipment and conducting training in areas where clinical trials are conducted. Universities can be established as research centers.

Competing Interests. It is important that clinical research activities not detract from existing resources or drain health services from other places.

Community Risk–Benefit. Communities can benefit from clinical trials if there are plans for posttrial implementation and drug access. General health care can be improved from infrastructure development, educational effort, and screening programs. Government and industry need to work in parallel to identify community needs and develop posttrial plans. Too much research in one area can be perceived as invasive or exploitive. Communities may become resistant to more research.

Sustainability. Once research is completed in an area, there should be sustainable resources/benefits, which can include equipment, drugs, knowledge, and add-on health services. When a clinical trial of a drug is conducted in a country, the drug should be made available in that country if the drug is effective.

Pretrial Negotiations. A number of issues should be discussed when designing/planning clinical trials: who determines/judges drug efficacy, what to do if a drug fails, positive outcomes versus negative outcomes, during-trial requirements, standards of prevention/care, and understanding what the sponsor is providing.

Proposed Action Items/Next Steps

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

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

Protocol/Contract Elements. Elements include posttrial drug access; mechanism for treatment or support for diseases, disorders, or conditions discovered during routine examination; long-term commitment; types of drug administration; and drug formulations (for example, manufactured versus extemporaneous).

Exploitation. Children should not be considered or used as a commodity in pediatric clinical trials. Pediatric trials should not leave benefits for others at the expense of pediatric populations, although there may be spin-off benefits for nonpediatric populations/communities (for example, developing infrastructure).

Role of Investigators, Ethicists, and Regulators. Because each country has its own regulations, there is a lack of harmonization among policies and regulations (for example, trial-related injury compensation, payment for experimental drugs, and research-related liability for malpractice). Investigators, ethicists, and regulators can encourage the pharmaceutical industry to recognize the importance of developing resources for community engagement, education, and awareness. These resources can provide a sustainable infrastructure.

Standards of Care. Local standard-of-care issues may affect the health needs of the research population. Local standards may not be good enough to ethically conduct a study. It may be a question of the ethical standards that are used. Global pediatric clinical trials may benefit from an "optimal" standard of care. The differences in standards of care from country to country allow different perspectives on what trials are considered ethical or unethical. The perspective on standard of care depends on the purpose of the clinical trial. There are issues of an unproven

standard of care. Some standards of care are used for conditions for which they are not licensed. In some circumstances, there are no data to support a standard of care. There are questions about acceptable levels of evidence for validating standards of care.

Information Dissemination. Investigators, ethicists, and regulators can play a role in disseminating research findings, particularly negative findings. Ethics committees may inquire about restrictions on an investigator's ability to publish. There is no accountability for publishing negative findings. At the very least, there should be feedback to the community (for example, community advisory boards) in which the research was conducted.

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)?

Major Issues

Background. Clinical capacity comes before a regulatory capacity. Without sufficient clinical capacity to conduct research, there is no need for regulatory capacity.

Gaps. Identifying gaps can help determine how countries can collaborate to build capacity and the kind of resources that are needed. Although solutions may be country-specific, a standard-format ethical–legal directory could provide a template for determining ethical, legal, and social responses to particular circumstances.

International Disasters. Disasters provide an opportunity for international regulators and IRBs to break down barriers to deploy resources, improve collaboration, and develop networks.

Knowledge Sharing. International cooperation in knowledge sharing about clinical research and training can help build international capacity. Knowledge sharing could include the sharing of data collection tools and clinical design concepts. A central repository for methodological approaches could be established. Raw data (for example, pharmacokinetic data) can be posted on the Internet to allow maximum use of data. However, investigators may be reluctant to share

protocol designs because they may be considered intellectual property. In general, there is cooperation in sharing protocols developed within networks but not outside of the networks.

Clinical Trialists. There needs to be a paradigm shift in the perception of clinical trialists. In academic settings, clinical trialists are not appropriately recognized for their participation in multicenter clinical trials. Investigators are discouraged from participating in clinical trials because they may not be able to publish papers or may have to wait years to publish papers. There are concerns about career development and getting credit for protocol development.

Data Collection and Reporting. Data collection and data submission to regulatory agencies should be harmonized internationally. There should be consistency in the way data are collected. Networks should identify the essential information to submit to regulatory agencies and work backward to ensure that the protocol is designed to collect this information. The data should be consistently reported. Networks should use the same forms and terminology. Funding agencies should state in requests for applications (RFAs) the questions to be answered in an effort to have networks or coalitions collaborate in collecting the appropriate data to answer the questions. The questions and funding then drive the networks' data collection.

Safety Reporting. Terminology for adverse events should be clearly defined in guidelines to ensure that adverse events are consistently described (including severity) and reported. A common language for adverse events should be developed for standardized guidelines.

Laboratory Standards. An area for potential development is lab standards and lab references.

Training. Another area for potential development is training for investigators and clinical study staff. Clinical trial research could be considered as a career path, which would encourage training in epidemiology, clinical trial design, biostatistics, and so on. Academic institutions such as the Fogarty International Center could foster this training. Training could include analysis of multiregional clinical trials. Pharmaceutical companies that sponsor trials also provide training and certification for clinical investigators. Training and certification among regulatory agencies (for example, the FDA), academic institutions, and pharmaceutical companies should be coordinated to avoid duplication.

Institutional Views on Clinical Research. Stand-alone institutes tend not to have much interest in clinical research. These institutes are more interested in basic science research. Hospitals tend to be more interested in patient throughput than clinical research. Research institutions and funding agencies tend not to be interested in clinical research.

Information Resources. Regulatory agencies (for example, the FDA) could develop an international list of recognized pediatric trials centers in each country and include contact information for the most appropriate person (that is, a "point person") to inquire about collaboration with those centers. RFAs issued by the European Union provide information on potential partners, who indicate areas of interest and expertise. Some agencies/organizations

develop lists of publically funded investigators, their areas of expertise and interest, and research experience.

Proposed Action Items/Next Steps

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

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

Background. The types of studies that the FDA and the European Medicines Agency (EMEA) are conducting are similar. The study data should be acceptable in both the United States and Europe to change labeling. The goals are to share data and not duplicate studies. Other countries may have different experiences in submitting study results to regulatory agencies for labeling changes.

Data Submission. Sometimes it is unclear at the beginning of a study whether data will be submitted for label changes. The question of label changes is, in some cases, almost an afterthought. Establishing research standards for pediatric clinical trials would help ensure that data collected across network study sites are consistent and acceptable for submission.

Good Clinical Practice (GCP). Pediatric trials should adhere to GCP. Site accreditation and certification could be considered. Investigators should be aware of regulatory agency requirements. Adhering to GCP requirements such as databases and data monitoring are challenging for some countries that may lack necessary resources. Minimal standards for data monitoring could be established. There are issues with standardization of specimen handing and storage.

Education. Clinicians/pediatricians need to know that labeling is important and that the reason drugs are used off-label is because there are no safety and efficacy data. Clinical researchers also need to know that labeling is important.

Expertise. In some countries, there is a lack of expertise among regulatory agencies and review boards and committees regarding pediatric clinical trials. Regulatory agencies in some countries

do not have the capacity to conduct technical reviews of protocols. International organizations may be able to provide technical reviews for such agencies.

Drug Approval Process. Drug approval is a sovereignty issue. The Division of AIDS has different memoranda of understanding with other countries to facilitate information exchange for drug approval processes while respecting sovereignty. The Division of AIDS has confidentiality arrangements that allow it to share information that is confidential and commercial but not trade secrets with EMEA, Health Canada, ICH partners, and other regulatory agencies. These data may be posted on a Web site in the future.

Summary. There is a need for training and education for investigators and study staff. There is a need for education of students who may want to pursue clinical research as a career path. Clinicians and researchers should be educated on the importance of labeling. There is a question of whether all clinical trials in pediatrics should be conducted according to GCP. Adhering to GCP standards would help ensure that results are interpretable across networks. For all pediatric clinical trials, there should be more uniform standards for data collection and reporting.

Proposed Action Items/Next Steps

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

Participants

Linda-Gail Bekker, M.B.Ch.B., D.C.H., D.T.M.&H., F.C.P.(SA)., Ph.D., Associate Professor, Institute of Infectious Diseases and Molecular Medicine, Desmond Tutu HIV Center, University of Cape Town, and the Desmond Tutu HIV Foundation, Cape Town, South Africa

Diane K. Brandt, Project Director/Principal Investigator, BPCA Data Coordinating Center, The EMMES Corporation, Rockville, MD, USA

Andrew Davidson, M.B.B.S., M.D., F.A.N.Z.C.A., Clinical Associate Professor, Department of Anaesthesia, Royal Children's Hospital, Melbourne, VIC, Australia

Patricia M. Flynn, M.D., Director of Clinical Research, Department of Infectious Diseases, Translational Trials Unit, St. Jude Children’s Research Hospital, Memphis, TN, USA

Sophie Fornairon, M.S., M.D., M.P.H., Head of Department, Therapeutic Marketing Authorisations Assessment, Direction of Medicinal and Biological Products, French Health Products Safety Agency, Saint-Denis, France

Norman Fost, M.D., M.P.H., Professor, Pediatrics and Bioethics, Department of Medical History and Bioethics, Department of Pediatrics, School of Medicine and Public Health, University of Wisconsin Hospital, Madison, WI, USA

Marta Fracapani, M.D., M.Bioethics, Director, Faculty of Medical Science, National University of Cuyo, Villa Nueva-Guaymallen, Mendoza, Argentina

Caroline M. Ibrahim, B.S., Head, Biologicals Registration Department, Central Administration of Pharmaceutical Affairs, Cairo, Egypt

Kader Kourad, M.D., Ph.D., Acting Chief, Clinical Evaluation Division–Autoimmune and Endocrinology, Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics, Biologics and Genetic Therapies Directorate, Health Canada, Ottawa, ON, Canada

Birka M. Lehmann, M.D., Head of Licensing, Division III, Federal Institute for Drugs and Medical Devices, Bonn, Germany

Feng-Ying (Kimi) C. Lin, M.D., M.P.H., Medical Officer, Program on Developmental and Molecular Immunity, NICHD, NIH, Bethesda, MD, USA

Mary Anne Luzar, Ph.D., Branch Chief, Regulatory Affairs Branch, Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID), NIH, Bethesda, MD, USA

Holly F. Lynch, J.D., M.Bioethics, Bioethicist–Contractor, DAIDS, Human Subjects Protection Branch, NIAID, Henry M. Jackson Foundation, Bethesda, MD, USA

Justina Molzon, M.S.Pharm., J.D., Associate Director for International Programs, Center for Drug Evaluation and Research, FDA, Silver Spring, MD, USA

Miguel A. Ramiro, Ph.D., Senior Lecturer, "Bartolomé de las Casas" Human Rights Institute, Universidad Carlos III de Madrid, Getafe, Madrid, Spain

Anna L. Ridge, M.B.Ch.B., M.P.H., Technical Officer, Medicines Access and Rational Use, Essential Medicines and Pharmaceutical Policies, World Health Organization, Geneva, Switzerland

Michelle D. Roth-Cline, M.D., Ph.D., Health Scientist, Ethics Program, OPT, Office of the Commissioner, FDA, Rockville, MD, USA

Bret J. Rudy, M.D., Vice Chairman of Pediatrics, Department of Pediatrics, New York University School of Medicine, New York, NY, USA

Hari C. Sachs, M.D., Medical Officer, Office of New Drugs, Immediate Office, Pediatric and Maternal Health Staff, FDA, Silver Spring, MD, USA

David Siegel, M.D., Program Director, Chemical, Biological, Radiological, and Nuclear Research Program, Obstetric and Pediatric Pharmacology Branch, Center for Research for Mothers and Children, NICHD, NIH, Rockville, MD, USA

Bo Sun, M.D., Professor, Department of Pediatrics, Children's Hospital of Fundan University, Shanghai, China

Ulrica M. Swartling, M.A., Ph.D., Senior Researcher, Faculty of Health Sciences, Division of Pediatrics, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

Masaaki Tsukano, M.Sc., Division Director, Division of Regulatory Cooperation, Office of International Programs, Pharmaceuticals and Medical Devices Agency, Chiyoda-ku, Tokyo, Japan