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 A Discussions

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

Purpose

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

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

Question 1

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

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

Major Issues

Terminology. According to one group member, "language is the most difficult part of scientific ethics." The group spent considerable time discussing terms for describing the risks and benefits of clinical trials participation.

Defining "Therapeutic Benefit." As the discussion group considered a potential guideline regarding the inclusion in clinical trials of children who likely will receive no direct therapeutic benefit, it explored the spectrum of benefits clinical trials may hold for individuals and their communities. Several group members alluded to obvious direct health benefits, such as access to

new treatments. The group spent considerable time discussing how potential indirect benefits should be weighted against potential personal risk. Indirect benefits discussed include improvements in health infrastructure and training of local health care staff. Other potential indirect benefits include the development of future therapies that may benefit individuals, their families, or their communities in the future. Several group members took issue with the widespread practice of sponsors conducting trials and then never marketing the resulting drug or therapeutic device in the host country. As a practical matter, however, most group members agreed that, at a trial's outset, ascertaining the likelihood of a therapy going to market in the host country is difficult if not impossible.

Defining "Risk." The group recognized that "risk" varies by nation, culture, and generation. For example in China, which has a one-child policy, parents and grandparents are very reluctant to allow children to participate in clinical trials that offer no direct benefit. China, therefore, would be considered to have a very stringent definition of risk. The group discussed the feasibility of articulating a global standard for measuring risk and whether it was indeed possible to agree internationally on terms to describe risk.

Defining "Healthy" Children. The group discussed the merits of the terms "healthy" and "at-risk" to describe children who would gain no direct benefit from participating in a clinical trial. The group contrasted "healthy" with the term "at-risk." Some of the group suggested "at-risk" was too broad a term and could be applied to nearly everyone.

Consent. The group discussed ways to facilitate the consent process, criteria for establishing consent, such as literacy, and the ethics of conducting research on children when obtaining consent is impossible, such as when studying extreme lifesaving therapies or transient conditions. Some group members argued for universally defined language in the documents that explain the risks and benefits of participating in a trial, so-called consent forms. Others pointed out the significant challenges of obtaining parental consent in some cultures. For example, in some African nations, only a father or community elder can give permission for a child to participate in a clinical trial.

Summary. Feelings were mixed regarding the inclusion of children who stand to gain little or no direct benefit through participation in clinical trials. The general consensus was that each trial needed independent evaluation.

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

The group generally agreed that withholding treatment from children was unethical. However, in many cases, determining at the outset of a clinical trial whether withholding treatment will cause serious harm is difficult to impossible. Some group members thought placebo-controlled trials were ethical in certain circumstances such as trials that effectively delay the administration of medications to children with recently diagnosed type 2 diabetes. "There is a difference between withholding medication and making a child sick," said one member of the group. Most thought it was better to compare active therapies. However, testing multiple therapies is often not feasible due to a limited number of trial participants. In addition, comparisons to existing therapies, which are often not evidenced-based therapies, hold limited usefulness.

Summary. A single set of guidelines that would apply to every placebo-controlled and randomized controlled clinical trial would be difficult to construct. The group generally agreed that the World Health Organization is poised to take a greater role in establishing guidelines for placebo-controlled and randomized controlled clinical trials in children.

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 different agendas be prioritized when designing and conducting pediatric trials?

Major Issues

Addressing the Needs of the Local Population. During the discussion, one group member identified three types of clinical trials: (1) trials that benefit the host population, (2) trials that benefit the sponsoring population, and (3) trials that benefit both. Many countries, including Canada and China, require that clinical studies benefit the local population. However, this often translates to establishing theoretical benefits, as sponsors often do not know at a trial's outset

whether the therapy under review will eventually become locally available. In addition, therapies that become locally available may be prohibitively expensive or otherwise inaccessible to individuals that participated in the trials. Some countries weigh indirect benefits, such as the building of new infrastructure to serve host populations, when a trial offers no direct benefits.

Summary. The group generally agreed that the risks and benefits of a clinical trial should be considered on their own merits and that promises of infrastructure should not be considered.

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

The group discussed the various ways nations evaluate ethics in clinical trials. Some countries rely on governmental health ministries, whereas other countries rely on ethics committees. Some countries, including Japan, have different criteria and processes for evaluating behavioral trials.

The group briefly discussed the merits of increasing communication among nations' ethics bodies. One group member suggested the formation of an international body with which all trial sponsors would be required to register. Databases, such as ClinicalTrials.gov, already contain such information, but they are frequently not up-to-date. However, simply listing trials provides no assurance against the exploitation of local populations.

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

Group members suggested a variety of ways to create new and expand existing research networks. Among the ideas discussed was the prospect of government agencies playing a stronger role in creating and maintaining clinical networks, particularly for trials evaluating older drugs, which are off-patent and not likely to be funded by private industry.

Another group member commented on the lack of participation or awareness of the need for pediatric clinical trials by pediatricians. "The pediatric community is often not very aware of issues in global pediatric clinical trials," said one group member.

Drug companies could make important contributions to research networks, said one group member. Research networks are often created to serve a specific trial and are then dismantled at the trial's conclusion, taking with them valuable information, infrastructure, and personnel. Although industry may be reluctant to participate in research networks, they may become motivated by the potential savings that networks offer.

Summary. The group proposed several ideas that might encourage the development of research networks, including efforts to involve more pediatricians in clinical research, legislation requiring sponsors to conduct clinical trials on all new drugs, the development of a research network template, and the integration of research with health care resources.

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

With clinical trial sites all over the world, researchers seek better ways of navigating local institutional review boards and regulatory requirements in an effort to streamline the clinical trials application process. One group member stated that relatively small issues, such as getting permission to import study medication, can cause major delays in clinical trials.

The group discussed the possibility of building international networks of investigators, who, based on their past trial experiences, could advise future clinical trials during both the application and implementation phases.

Currently in existence are many specialist networks that focus on specific diseases. A remaining challenge, commented one group member, is creating "mixed" networks for drugs or diseases that would not fit into a specialist network.

Efforts aimed at expediting pediatric clinical trial applications are currently under way at the NIH, according to one member of the group. Africa, however, currently has no pediatric research networks. A network of five major children's hospitals in China recently applied to the Chinese Food and Drug Administration. Although Chinese researchers are eager to conduct pediatric clinical trials in children, regulators view adult trials as surrogates. Europe is building a pediatric research network, which includes not only pediatricians but also general practitioners, who often administer care to children.

One member cited communications between the FDA and the European Medicines Agency (EMEA) as an example of a very productive regulatory collaboration.

Proposed Action Items/Next Steps

Ideas suggested at the meeting included choosing a current, ongoing clinical trial for regulators and researchers to evaluate, streamline, and showcase as a model for other investigators; building an information database containing tips based on the experiences of former researchers; greater use of information technology; and distance learning programs to give local health care providers training in running clinical trials. An important action item is to build a database of senior researchers who could be consulted by regulatory authorities (for example, through teleconferencing) about specific questions. Such consultations would support pediatric-specific regulatory networks in developing countries.

Participants

Laura Arbour, M.D., Associate Professor, Medical Genetics, University of British Columbia, Vancouver, BC, Canada

Leslie K. Ball, M.D., Director, Division of Scientific Investigation, Office of Compliance, Center for Drug Evaluation and Research, FDA, Silver Spring, MD, USA

Ana Valeria Bertaina, M.D., Physician, National Administration for Medicine, Food, and Medical Technology, Lujan, Buenos Aires, Argentina
Ann Farrell, Ph.D., Professor and Head, School of Early Childhood, Queensland University of Technology, Kelvin Grove Campus, Brisbane, QLD, Australia
Alessandro Ferreirado Nascimento, B.S., Specialist, Coordination of Clinical Trials, National Agency of Sanitary Surveillance, Aguas Claras, Brasilia, Brazil
Michio Fukumizu, M.D., Ph.D., Reviewer, Office of New Drug III, Pharmaceuticals and Medical Devices Agency, Chiyoda-ku, Tokyo, Japan
Rohan Hazra, M.D., Medical Officer, Pediatric, Adolescent, and Maternal AIDS Branch, NICHD, NIH, Bethesda, MD, USA
Kalle Hoppu, M.D., Ph.D., Medical Director, Poison Information Centre, Helsinki University Central Hospital, Helsinki, Finland
Chingli Hu, M.D., Professor, Pediatrics Department, Shanghai Jiaotong University School of Medicine, Ruijin Hospital, Shanghai, China
Diana Koh, B.Sc., Senior Regulatory Specialist, Clinical Trials Branch, Health Sciences Authority, Singapore, Singapore
Lucie Krávačková, M.D., Assesor, Clinical Trial Unit, Department of Clinical Trials, National Authority–State Institute for Drug Control, Prague, Czech Republic
Jaclyn K. Marshall, B.S., Consultant, The Lewin Group, Eden Prairie, MN, USA
Hidefumi Nakamura, M.D., Ph.D., Director, Division of Clinical Research, National Children's Medical Center, National Center for Child Health and Development, Setagaya-ku, Tokyo, Japan
Robert M. Nelson, M.D., Ph.D., Pediatric Ethicist, OPT, Office of the Commissioner (OC), FDA, Rockville, MD, USA
Viveca A. Odlind, M.D., Ph.D., Professor, Medical Products Agency, Uppsala, Sweden
Jennifer S. Read, MD., M.S., M.P.H., D.T.M.&H., Medical Officer, Pediatric, Adolescent, and Maternal AIDS Branch, Center for Research for Mothers and Children, NICHD, NIH, Bethesda, MD, USA
Annette Rid, M.D., Postdoctoral Fellow, Department of Bioethics, NIH, Bethesda, MD, USA
Lainie F. Ross, M.D., Ph.D., Carolyn and Matthew Bucksbaum Professor of Clinical Ethics, Pediatrics, Medicine, and Surgery, MacLean Center for Clinical Medical Ethics, University of Chicago, Chicago, IL, USA
John A. Rossi, V.M.D., M.Be., Commissioner's Fellow, OPT, OC, FDA, Rockville, MD, USA
Seema K. Shah, J.D., Bioethicist, Division of AIDS, National Institute of Allergy and Infectious Diseases, NIH; Department of Bioethics, NIH, Bethesda, MD, USA
Hans W. Stoetter, Dr.med., Division Clinical Review, Sector Marketing Authorisation, Swissmedic, Berne, Switzerland
Jean W. Temeck, M.D., Lead Medical Officer, OPT, OC, FDA, Rockville, MD, USA
Paolo Tomasi, M.D., Ph.D., Scientific Administrator, Human Pre-Authorisation Unit, Scientific Advice, Orphan Drugs, and Pediatric Medicines Sector, EMEA, London, UK
Evans K. Tusubira, M.S., Medical Doctor, Clinical Trials, Drug Information Department, Secretariat/Head Office, National Drug Authority, Kampala, Uganda
Mi-Ok Yun, Ph.D., Deputy Director, Cardiovascular and Neuropharmacological Drugs Division, Drug Evaluation Department, Korea Food and Drug Administration, Seoul, South Korea