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
Summary of Breakout Group D Discussions

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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

Participants discussed the issue of how best to characterize risk and benefit in different countries and for different types of trials. For example, what is the benefit for a placebo control group in trials of vaccine for childhood infection? Participants agreed that there is a need to clarify group risk–benefit versus individual risk–benefit; will some children be unprotected or not helped?

Participants discussed the gradation of risk: what level of risk is acceptable when a study promises no immediate direct benefit? What is "low" risk? Is it possible to establish an international standard or is acceptable low risk defined situationally, and is it different in an

urban North American setting than in a rural India village? If there is no international standard, is it possible to impose higher risk on a country-by-country basis? Is acceptable local relative risk higher in developing countries?

Participants agreed that risk and benefit must be considered separately and that identifying correct study populations is a central difficulty. International guidelines cannot include "daily life" risk. Participants agreed that international clinical trials are not possible without an ethically acceptable common understanding of risk. Is it possible to develop gradations of risk, such as "minimal" and "minor?" Is this incremental definition a basis for an international standard?

Participants agreed that international guidelines should provide a common understanding and a point for anchoring discussions. International guidelines are necessary but may not eliminate national standards.

Regardless of any international standard, in any clinical trial informed consent must be obtained and ethical review conducted, without exception. Risk must be identified, and risk management must be explained before the trial begins. Acceptable risk must be evaluated on a country-by-country basis for trials that may lead to a group benefit but not to therapeutic benefit for individual participants. Risk is relative. For example, x-rays can kill, yet are a comparatively small risk in developing countries.

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

Participants discussed ethical questions associated with placebo arms in trials that may involve a treatment understood to be the best available. What disclosure and counseling is necessary? It may not be possible to derive any useful information without placebo control, but if a standard therapy produces known results, this should be available to children. Participants agreed that risk is a vague concept unless it is considered in a specific context, and the standard should not be different for children than for adults. Participants or parents must understand that the active arm

may have some risk if the trial involves a study drug approved for adults but not yet tested in children.

In adults, an established standard is "no serious harm" from placebo assignment. This is different from benefit. Should this be the standard for children? A placebo may be the only way to identify medications that are a proven therapy in adults but may have no effect in children. Informed consent requires an explicit understanding by parents and children that placebo will not provide any individual benefit, though it may contribute to improved treatment.

Participants noted that risk and benefit may not be determinative factors in trials. Tests of antivirals, for instance, may evaluate surrogate markers, and small single arm studies are possible for conditions such as infectious disease.

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

Participants noted that the ethical problem implicit in the question revolves around a hypothetical drug that may not become available as treatment in the trial population. Actual experience, however, shows that treatments once unavailable in some countries, such as AART in Tanzania, can become a standard treatment. Ethical considerations should be based on general relevance, not when trial drugs might be marketable or otherwise available.

Participants discussed HIV/AIDS trials as an example, noting that most are now multicountry, multisite trials and are broadly generalizable. "Opportunistic" clinical trials that leave minimal advantage for host populations are becoming rare. Trials that involve a combination of immediate or near-term benefits for regions and participants are the norm. Networks and collaborations make trial information accessible to local and regional interests. It is important to address the needs of local stakeholders. Local needs should be incorporated into trial design.

In South Africa, collaboration is an important element and local needs are addressed insofar as it is possible in negotiating terms of the trial. Other mechanisms can be negotiated to ensure a local benefit, such as building local clinics to provide basic health care.

What would be the result if a trial group left its host locale and the drug did not later become locally available, but some participants benefitted while the trial was ongoing? In some respects this situation could have a worse local effect than if no trial had been conducted at all. Trial approval should require an assurance of availability.

Sometimes a research site can reap important benefits that reach the general population. There is a local "payback" even though a pharmaceutical company might not agree to any posttrial commitment. Participants discussed examples such as establishment of educational networks and materials and local clinic improvements. Do these advantages offset the fact that a treatment or trial drug does not have local relevance?

How can these issues be prioritized? In one region the local benefit may be improved health care, in another location it may be jobs or infrastructure. "Benefit" might mean something other than improvement in health, but negotiation of trial design should require that the tester address a local need. In Canada, for example, negotiations sometimes involve access to data for trials that have no immediate local relevance.

Consideration of local benefit is, in part, a question of global social justice. Minimum benefit necessary to achieve a given result is not sufficient in all cases.

Can this issue be addressed in the same way for for-profit trial organizers as for research/public institutions? Does the argument reduce down to extracting as much as possible from the deepest pockets?

From the perspective of developing African countries, local needs must be addressed—if not health benefits, then capacity development or similar considerations. In the developing world there is an endless need and many avenues for improvement. Priorities must be set at the local level among all stakeholders. Local benefit should be a requirement. Availability must be the first priority, but local discussion and dialogue are essential in setting case-by-case priorities.

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

Participants felt the question is vaguely worded, but agreed that a relevant discussion should focus on what is important to an individual child in the trial, based on experience. Is routine health care mandated as part of the trial? What if a participating child has an unrelated but treatable condition such as earache or asthma?

Does this implicit obligation continue after a trial and follow-up are completed? Perhaps trial and posttrial obligations should be specified. Is it possible to draw ethically defensible distinctions between a population where health care is generally accessible, whether in trial or not, and a population where care is only available as a condition of trial. To what extent does a treated or untreated child represent the general population and therefore reflect on the value of trial findings?

Might treatment be used as a coercive tool to "buy" consent, thereby calling into question the legitimacy of a trial population? Or is coercion not an apt description of choosing between options of varied "desirability?" Would decision to participate be the same for a child with excellent health care, adequate health care, substandard health care, or none at all? May a trial design provide absolutely minimal care because it is better than none?

Participants agreed that the key issue in addressing this question is dialogue at the local level, and the "correct" answer is always defined by local conditions. Those closest to patients are best able to articulate the needs, and they must have a voice on institutional advisory boards (IRBs) and in study design. IRBs must ask these questions, and ethics and other review boards must follow up.

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

The model for interrelated networks exists within national health structures. Pediatric-focused structures at the national level are important, and coordination should harmonize various national networks. Some European Community networks are in place and could serve as models. European Union intergovernmental coordination is more advanced than elsewhere, where research groups and centers exist but are not integrated into networks.

Canada has less advanced networks for mother–child issues, and some specific pediatric centers have been established. Oncology issues are another focus. These are not federally funded but are national in scope.

Efforts are under way in Australia to integrate relevant research groups into larger networks to better promote the needed pediatric medicines research. Some existing networks have origins in a clinical care focus (with variable research activity), whereas others are focused primarily on research. There is currently no specific plan addressing how to bring together existing pediatric networks in a way that would help focus activity on clinical trials of medicines. These efforts would benefit greatly from federal commitment, including appropriate resourcing, national coordination, and relevant capacity building.

Australia is currently also in the midst of developing a nationally harmonized human research ethics review system. The special considerations for the appropriate review of pediatric clinical trials have not yet been systematically addressed as part of this initiative, but discussions are under way. These would be helped greatly by the development of a globally harmonized guidance addressing ethical considerations for pediatric clinical trials.

The International Maternal Pediatric Adolescent AIDS Clinical Trials group is an example of a well-developed and flexible network based on priorities, not specific clinical specialties.

Networks should incorporate centralized organization and design, with local research networks interacting to develop trials that are centrally funded and administered. In many countries, national support is more likely to be available for structure only, not research or local resources. A centralized resource base may be used to create important infrastructure such as well-developed Web-based linkages and data housing.

Development of wide networks may be possible by "adding on" to existing single-issue networks.

The goal should be an independent pediatric-specific network, not a mesh of pediatric elements drawn from other existing networks. Efforts should not discourage associations that can be created among existing nonspecific networks or sap resources from existing structures.

There is no need to invent a network structure from the ground up. A model might be evolution of children-specific networks from more broadly structured networks (children's cancer networks emerging from more general cancer research networks).

Development of networks must begin at the level of personal involvement by pediatricians or clinical investigators. Successful networks require drive "from within"—this energy cannot be artificially imposed. Once a network is under way, national support for infrastructure is important. Political will is essential to sustain the effort. The optimal approach would be a combination of top-down (federal) and bottom-up (clinician/researcher-driven) steps.

National support must be for networks, not merely individual research portfolios that advance the issue. Robust networks can incorporate research from industry, academia, and government sources.

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

Initial steps should be conversations and formal meetings among regulators and research interests. The regulatory environment is dominated by large advanced countries. Perspectives and circumstances of less developed countries are essential.

Issues incorporated in the Declaration of Helsinki should be addressed in the process of establishing networks.

In Africa, existing regional collaborations on issues other than health may provide a platform for developing regulatory cooperation.

There currently is no pediatric-specific regulatory approach in Canada. As trials become increasingly globalized, the need for pediatric-specific global regulation becomes more important. Without specific structure, "urgent" issues will distract focus from "important" pediatric issues.

Regulatory capacity building is critical.

It will be important to identify core areas of expertise that can be incorporated into definitions of minimum required conditions of pediatric research, including for its appropriate design, ethical review, and conduct.

Trial-specific modifications on some aspects should be anticipated in any structure. Guidelines and frameworks should allow for flexibility but specify basic requirements.

The World Health Organization (WHO) includes a branch that supports training. This resource might contribute to capacity building through an approach that is more efficient than repeated hospital-by-hospital trainings. WHO needs to be prodded by member states but will respond to a clear call.

Proposed Action Items/Next Steps

Specific steps that might be taken to begin establishing pediatric-specific initiatives include:

- Establishing an international Web site
- Extending regional collaborations on a more global scale
- Adding program/agenda elements to international meetings
- Involving WHO as a supporting resource
- Expanding educational opportunities in developing countries to help researchers and clinicians better understand the regulatory environment
- Incorporating pediatric-specific terms into agreements that approve trials or product marketing.

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