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SYMPOSIUM

Ethical Issues in International Vaccine Research and Development

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In this discussion of the ethics of multi-national vaccine trials, I will refer primarily to the UNAIDS Guidance Document, Ethical Considerations in HIV Preventive Vaccine Research (hereafter, Guidance Document) [1]. This document, which was developed in the mid-1990s, states that its scope is limited to multinational trials of HIV preventive vaccines. However, I suggest that it is more generally relevant to multinational trials, or development programs, for vaccines. This Guidance Document was influential in the development of another major document which provides ethical guidance and direction for research involving humans as subjects, the CIOMS† (Council of International Organizations of Medical Sciences) International Ethical Guidelines for Biomedical Research Involving Human Subjects (hereafter, International Ethical Guidelines) [2] and, indirectly, the World Medical Association's Declaration of Helsinki (hereafter, Helsinki) [3].

ETHICAL UNIVERSALISM VS. CULTURAL PLURALISM

When one is working to develop ethical guidelines in the international arena, one is immediately confronted with one of the classical questions in ethics: Are ethics universal or do they differ from one culture to another? One might be able to escape this question when working locally or within the confines of a relatively homogeneous culture, but not in the international context [4]. Ethical universalism is a position that holds that ethics, or ethical principles, are the same in all places and in all times. Universalists note that ethics seem to be evolving over the years, but the people who have a strong commitment to universalism hold that this is just an indication that we're getting closer and closer to the universal truth. Cultural pluralism — in contrast to universalism — notices that ethics are, after all, developed in the course of conversations within specific cultures,

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†Abbreviations: CIOMS, Council of International Organizations of Medical Sciences; IRB, internal review board.

and they necessarily reflect the histories and traditions of those cultures. Cultural pluralists conclude that differences in ethics across cultures are both inevitable and legitimate. Cultural pluralists sometimes refer to universalists with the derisive term, ethical imperialists. Some universalists similarly disparage pluralists by calling them ethical relativists.

My position is one of compromise: I believe there are some ethical principles that appear to be universal, particularly when they are stated at a highly abstract level. However, I believe that there is also a large degree of legitimacy in cultural pluralism. Even the universal ethical principles may be interpreted very differently in diverse cultures. What it means to show respect for persons in the United States may be vastly different from what it means in Sub-Saharan Africa. In my own work in the development of international ethical codes and guidelines, I aspire to what I call "'global applicability." That means that the guidelines are, as far as we can tell, applicable currently in all the cultures and societies in the world. There is an assumption that we will be revising these guidelines from time to time as new understandings come to the fore.

SUBSTANTIVE AND PROCEDURAL NORMS

A substantive norm is a rule that specifies what one should do because it is morally right to do so; similarly, such rules may specify what one should not do because it is morally wrong to do so. Procedural rules specify what procedures one should follow. Some define the procedures one should follow to determine what to do when substantive rules do not give clear guidance as to what specific behavior is called for in a particular situation. Other procedural rules provide support or assistance as one attempts to comply with the requirements of a substantive norm. An example of the first type of procedural rule is the requirement for review and approval of all research proposals by an institutional review board (IRB); the purpose of this procedure is to assure compliance with ethical rules and to see to it that the requirements of ethical norms are interpreted appropriately in particular circumstances. The requirement for a consent form is a procedural norm of the second type; it helps the investigator remember all the elements of information that must be divulged during the process of informed consent. (The requirement for informed consent, itself, is a substantive norm; it is required because it is morally right to provide prospective subjects with information that will empower them to protect their own interests.)

When developing guidelines for relatively homogeneous populations, one can include a relatively large proportion of substantive norms. Guidelines for heterogeneous populations, by contrast, are characterized by a higher proportion of procedural norms. It is much more difficult to specify substantive norms when dealing with the diversity of circumstances and cultural traditions that globally applicable guidelines must accommodate.

CAPACITY BUILDING

The UNAIDS Guidance Document and the CIOMS International Ethical Guidelines each devote considerable attention to multinational research in which the sponsors are located in the wealthy industrialized countries and the research subjects are in low-resource countries; the latter are referred to as "host countries." The UNAIDS Guidance Document insists that the research should be limited to countries and communities that have the capacity for independent scientific and ethical review. It specifies that "the capacity must be adequate before the research begins" [1]. This, I believe, is an "aspirational" standard. An aspirational standard is one that we hope will be applicable sometime in the future; we must, however, acknowledge that this

standard cannot be followed today. This requirement is not in the CIOMS document. Implicit in the CIOMS International Ethical Guidelines is an understanding that we should be striving in that direction. Meanwhile, according to CIOMS (Guideline 20), sponsors and investigators from the wealthy industrialized countries "have an ethical obligation to ensure that biomedical research projects…contribute effectively to national or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research. Capacity building may include, but is not limited to…establishing and strengthening ethical review processes/committees; strengthening research capacity; developing technologies appropriate to health-care and biomedical research; training of research and health-care staff and educating the community from which research subjects will be drawn" [2].

Capacity building is required to ensure the scientific and ethical conduct of research. It also should be designed to foster meaningful self-determination for the communities in which the research is carried out, as well as for the individuals who serve as subjects. There is in all of the international documents, a strong recommendation that we should be striving to develop partnerships of equals and that the people from the wealthy industrial countries should be regarded as the moral equals of those in the host countries.

COMMUNITY ENGAGEMENT

Engagement of the community is designed to develop the vaccine development program as a collaboration involving the sponsors, investigators, community leaders, prospective subjects, and other stakeholders as appropriate. One major goal of community engagement is to ensure the acceptance of the research and development by the community in which the research is to be carried out. All aspects of the research program are to be discussed — even the scientific design of the protocols. Opinions of the community's members about the scientific and logistical features should be solicited and the wishes of the primary stakeholders should be accommodated to the extent this is feasible without compromising scientific validity. There should be a discussion leading to the design of risk reduction interventions and the development of effective methods of dissemination of information about the trial. Community engagement should also be designed to develop the informed consent process, to ensure equity in the choice of subjects, to reach agreements regarding the standards of care for research subjects who get sick during the course of a clinical trial, and to develop plans for the distribution of the vaccine in case it proves to be suitably safe and effective; the latter includes reaching agreements about the meaning of "reasonable availability" for the particular vaccine development program (see below) (infra).

EARLY PHASE VACCINE TESTING

The 1993 version of the CIOMS International Ethical Guidelines contained a requirement that the early phases of vaccine research (phase one and perhaps phase two) should be carried out in the country of the sponsoring agency [5]. This requirement was designed to protect the low-resource countries and communities from exploitation. Since the 1970s there has been a general expectation reflected in the ethical codes and guidelines that special justifications are required to involve vulnerable populations in research programs in which there are serious risks presented by interventions or procedures that do not hold out the prospect of direct benefit to the individual subjects [6]. Among the special justifications that might be considered are that the strain or clade of virus does not exist in the country of the sponsor, and the conduct of the early-phase

vaccine development in the developing country could be seen as a capacity-building experience to get the people in the host country accustomed to doing this kind of research.

The requirement to conduct early-phase vaccine research in the country of the sponsor was relaxed in the UNAIDS Guidance Document and the 2002 revision of the CIOMS International Ethical Guidelines. This change was in response to protests presented at the conferences that led to the development of the UNAIDS document. Participants from the low-resource countries protested that the CIOMS position on the developing countries was highly paternalistic. They noticed, in particular, that the guidelines for doing research in developing countries looked almost exactly like the guidelines for doing research involving children. They argued that they were not to be treated as children. In particular, they should be entitled to decide what sorts of research will be carried out in their countries.

RESPONSIVENESS TO THE HEALTH NEEDS AND PRIORITIES OF THE HOST COUNTRY

Research carried out in a low-resource country by sponsors and investigators from the wealthy industrial countries must be responsive to the health needs and priorities of the host country. This standard, which first appeared in the CIOMS International Ethical Guidelines in 1993 [5], distinguishes health needs from priorities. Health needs of a country could be determined by an outside agency. This agency could review epidemiological data and decide that since many people are afflicted by a certain disease, the country "needs" a means to treat or prevent the disease. Priorities, by contrast, are determined by the appropriate authorities within the country. Such authorities may decide that although the country has multiple "needs," they will assign a high priority to only one or two. Decisions about priority must take into account factors other than disease incidence or prevalence such as limitations in the country's resources.

JUST DISTRIBUTION OF BENEFITS

The products of multinational research carried out in low resource should be made reasonably available to the residents of the host country., This concept was introduced into international documents in the 1993 version of the CIOMS International Ethical Guidelines [5]. It has been included in subsequent promulgations by UNAIDS, the World Medical Association and CIOMS [1-3]. Originally, it was designed to apply to the therapeutic, diagnostic, or preventive products of the research. Subsequently, it has been interpreted to mean as well the new knowledge developed as a result of research. The reasonable availability standard sounds fine in the abstract; however, in particular cases, it has been very difficult to decide whether reasonable availability should apply only to the individuals who participate as subjects in the trials, whether it should apply more broadly to the entire host community or country, or whether it should apply to all populations at high risk for developing whatever disease is the target of the research. Moreover, it remains to be determined whether "reasonably available" could mean simply marketing the product in the host country or making it available at a price that is within the means of the host country. Although we cannot define what "reasonable availability" means in general, there is a consensus that its meaning within a particular research context should be agreed in advance among the primary stakeholders in the research program; this agreement should be negotiated during the process of community engagement.

"Sustainability" is another criterion for ethical justification of research designed to develop a therapeutic, diagnos-

tic, or preventive product. "Sustainability" refers to the ability of the host country to continue to make the product available to the residents of the host country after the research has been completed and the sponsors and investigators have departed, taking with them the extra funds and other resources typically made available during the conduct of the research. If the host country cannot sustain the use of the product, it is an indication that the researchers may not have been adequately compliant with the requirement for responsiveness to the health needs of the country [7].

PLACEBO CONTROLS

Placebo controls are ethically acceptable when there is no established vaccine for the indication for which the candidate vaccine is to be tested [1-3]. In some placebo-controlled vaccine trials, it may be appropriate "to provide for those in the 'control arm' a vaccine that is unrelated to the investigational vaccine" [2, Guideline 11]; for example, BCG. When there is an established vaccine, one requires a compelling reason to use placebo controls in a new vaccine trial. Such reasons might be that the established vaccine is not believed to be effective against the strain of virus that prevails in the host country, or convincing evidence that the biological conditions during the initial vaccine trial differ to the extent that the results can not be applied confidently in the new host country.

PROVISION OF HEALTH-CARE SERVICES

According to the CIOMS International Ethical Guidelines:

> External sponsors of research are ethically obliged to ensure the availability of health-care services that are essential to the safe conduct of the research; treatment for subjects who suffer injury as a consequence of research interventions; and services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned [2, Guideline 21].

In the commentary on this guideline, CIOMS states: "Although sponsors are, in general, not obliged to provide health-care services beyond that which is necessary for the conduct of the research, it is morally praiseworthy to do so. Such services typically include treatment for diseases contracted in the course of the study. It might, for example, be agreed to treat cases of an infectious disease contracted during a trial of a vaccine designed to provide immunity to that disease, or to provide treatment of incidental conditions unrelated to the study…."

> When prospective or actual subjects are found to have diseases unrelated to the research, or cannot be enrolled in a study because they do not meet the health criteria, investigators should, as appropriate, advise them to obtain, or refer them for, medical care.

The UNAIDS Guidance Document [1, Guidance point 16], in its specific consideration of the development of HIV preventive vaccines, states that those who become infected with HIV during the course of a clinical trial should be treated at one of three levels: 1) the level of care that would be offered in the country of the sponsor; 2) a level to be decided by the host country; and 3) a level consistent with that available in the host country. The level to be employed in any particular trial should be agreed during the process of community engagement before the trial is begun. It is not clear whether this guidance is applicable to clinical trials of vaccines other than those designed to prevent HIV infection.

INFORMED CONSENT

In some cultures and societies, informed consent may be problematic for any of several reasons; the following are

some examples. In many cultures informed consent is unfamiliar because it is not part of the customary interactions between health-care professionals and patients. Many or most of the prospective subjects may be unfamiliar with such concepts as cause and effect relationships, contagion, placebos, randomization and double-blind. In some communities, it is required that an individual must have the approval of a third party or of a group before making the sorts of decisions required in the process of informed consent. These points notwithstanding, UNAIDS [1, Guidance Points 12-15] requires individual informed consent in each case except when the subject is incompetent or incapacitated; in such cases third-party permission may be acceptable. UNAIDS requires that the process of informed consent be monitored. CIOMS [(2]) similarly requires informed consent or third-party permission; however, monitoring is not required.

SELECTION OF SUBJECTS

UNAIDS's requirements for selection of subjects in such a manner as to assure the equitable distribution of risks and benefits are generally harmonious with those embodied in most contemporary ethical codes and regulations. I will comment on several distinctive features of these requirements. First, as mentioned earlier, "low-resource" or "technologically-developing" countries are not to be regarded as generally vulnerable. The developed/developing distinction:

> …refers primarily to economic considerations, which are not the only relevant factors in HIV vaccine research. It also establishes two fixed categories, whereas, in reality, countries and communities are distributed along a spectrum, characterized by a variety of different factors that affect risk. It is more useful to identify the particular aspects of a social context that create conditions for exploitation or increased vulnerability for the pool of participants that has been selected [1, Guidance Point 7].

"Women, including pregnant women, potentially pregnant women and breast-feeding women, should be eligible for enrolment in HIV preventive vaccine trials, both as a matter of equity and because in many communities throughout the world women are at high risk of HIV infection" [1, Guidance point 17]. Similarly, "Children, including infants and adolescents" should be eligible for enrolment [1, Guidance point 18].

ECONOMIC CONSIDERATIONS

Several features of these guidelines create a potential for serious economic distortions. For example, provision of free medical services may be seen as an undue inducement to subjects, as well as to the host country. Often in the course of a clinical trial of a new vaccine, subjects receive medical goods and services that they simply would not get in the absence of research. Sometimes the research sponsor develops elaborate facilities to provide health care during the course of the research; local health authorities see this as an opportunity to redirect their efforts and resources. Then, when the research has been completed and the sponsors and investigators leave, the people of the community are even worse off than they were before the trial started because they do not even have what they had before the ministry of health withdrew its resources. Sponsors and investigators must be careful not to leave the host country worse off than it was before the research program began.

The requirement for reasonable availability may also be seen as an undue inducement both to the subjects and to the country. How else could residents of some Sub-Saharan countries be assured of continuing access to a vaccine or a drug that costs more than the annual per capita health budget in that country? Reasonable availability may also have an effect on the sponsor. If the reasonable availability stan-

dard were interpreted to require making the developed product reasonably available to all persons residing in the country, the prudent sponsor would very much prefer to conduct the research program in countries with relatively small populations.

CLOSING COMMENT

The distribution of wealth among the nations of the world is clearly inequitable. There is a temptation to use international research documents as devices to correct inequities. And I believe that, to some extent, this is a reasonable and constructive activity. However, I also believe that we must avoid the development of guidelines that would impede the efforts of sponsors and investigators in industrialized countries to assist countries with lesser resources in their efforts to develop treatments and preventions that they can afford.

REFERENCES

1. UNAIDS. Guidance Document: Ethical Considerations in HIV Preventive Vaccine Research. May 2000. (Accessed May 30, 2006 at http://data.unaids.org/Publications /IRC-pub01/JC072-EthicalCons_en.pdf)
2. Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Biomedical Research Involving Human Subjects. 2002. (Accessed May 30, 2006. at http://www.cioms.ch/frame_guidelines_nov_2002.htm.)
3. World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. 2004. (Accessed March 16, 2006, at http://www.wma.net/e/policy/b3.htm.)
4. Levine RJ. International codes and guidelines for research ethics: a critical appraisal. In: Vanderpool HY, ed. The Ethics of Research Involving Human Subjects: Facing the 21st Century. Frederick, Maryland: University Publishing Group; 1996: pp 235-59.
5. Council for International Organizations of Medical Sciences (CIOMS) in Collaboration with the World Health Organization: International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva, Switzerland: CIOMS; 1993.
6. Levine RJ. Ethics and Regulation of Clinical Research, 2nd ed. New Haven, Connecticut: Yale University Press; 1988.
7. Levine, RJ. Revision of the CIOMS International Ethical Guidelines: a progress report. In: Levine RJ, Gorovitz S, and Gallagher J, eds. Biomedical Research Ethics: Updating International Guidelines: A Consultation. Geneva, Switzerland: CIOMS; 2000: pp 4-15.