

Ethical Issues in the Design and Conduct of HIV Vaccine Trials

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Although of crucial importance, human trials of HIV vaccines should not go forward without appropriate attention to ethical considerations. This chapter provides an overview of the ethical considerations that arise in the design and conduct of clinical trials of preventive HIV vaccines.¹ The primary focus of this chapter is on Phase III (efficacy) trials; however, many ethical issues relevant to early stage (Phase I and II) clinical trials and to the marketing of HIV vaccines are also addressed.

This chapter begins with a review of some basic ethical principles and background information about clinical trials. The chapter then discusses ethical issues in clinical trial design, sample selection, informed consent, trial termination, and compensation for adverse reactions. The chapter concludes with a discussion of ethical issues relevant to clinical trials in developing countries, and issues arising from the incorporation of HIV vaccines into clinical practice.

BASIC ETHICAL PRINCIPLES

All biomedical research should be conducted in a manner that seeks not to violate three primary bioethical principles: 1) beneficence, 2) respect for autonomy, and 3) justice (3).¹ The principle

¹ This paper is concerned with *ethical* obligations, rather than *legal* ones. Ethical obligations tell us how we ought to act, in accordance with a series of morals, values, and principles. In certain contexts, including in the research context, organizations have put forward codes of behavior to guide ethical conduct. Typically, these codes are not binding legally, and at most, carry weight in determining the standard of care. Legal obligations tell us what we are required to do, in accordance with a government's legal system, as defined by regulations, legislation, and court decisions. Breach of legal obligations typically results in specified penalties.

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of beneficence addresses one's obligations to ensure the well being of others. Included within the principle are both the obligation to do no harm (called nonmaleficence) and the obligation to do good. In the context of clinical trials, the principle of beneficence requires that the welfare of research participants be protected. Participants must not be exposed to undue or excessive risks. This obligation may not be waived merely by informing subjects of these risks.

Moreover, initial responsibility for ensuring that risks are not excessive lies with the investigator, the vaccine sponsor, and an external review board. This responsibility may not be delegated to the research participant, for two reasons. First, research volunteers are unlikely to understand the risks of research as well as do the investigators and research sponsors. Second, it is a central tenet of research ethics that, unless personal benefit can be gained from trial participation, there are certain risks that are just too great for anyone to consent to, regardless of one's level of understanding of those risks. In trials involving human research subjects, an external review board, in collaboration with the investigators, is charged with assessing whether a given level of risk is justified. External review boards are given this responsibility because of concern that investigators directly involved in the study have interests that may bias their assessment of research risks. Also, external review boards typically include lay persons and persons from disciplines other than that of the investigator, who provide balance in the assessment of the reasonableness of risks.²

There are further obligations arising out of beneficence. When persons are included in research who might be particularly vulnerable to being exploited (e.g., prisoners, children, persons with little formal education), beneficence requires us to provide special protections to ensure that these participants are not harmed by the research.

Respect for autonomy, or respect for persons, obligates investigators to recognize research sub-

jects as individuals who have the right to make their own decisions, even when those decisions are based on values or world views that are different from those of the investigator. The doctrine of informed consent (described below) is derived from the principle of respect for autonomy.

Justice requires fairness in the distribution of both benefits and burdens. In research, this requires that no individuals or populations bear a disproportionate share of the risks of research without justification, and that all populations have access to the benefits of research participation.

Each of these three principles create independent obligations that may conflict. For example, decisions about what is the "reasonable" level of risk above which participants cannot be exposed (based on beneficence) may conflict with the right of potential participants to determine this level for themselves (based on respect for autonomy). Another example is the potential conflict among the obligation of external boards to protect certain groups or individuals from research risks (based on justice), the obligation to allow individuals to make that assessment for themselves (autonomy), and the obligation to obtain findings that will benefit society as a whole (beneficence). There are no clear rules for balancing these obligations. In actual practice, the investigators and an outside board first determine what harms are unreasonable. If the risks of trial participation are not unreasonable, potential research participants must provide "informed consent" to trial participation—research participants should be given information about the trial in question, including its risks, and allowed to decide whether they wish to participate, according to their own values and preferences.

CLINICAL TRIALS OF VACCINES

There are two main categories of vaccines being developed for HIV: prophylactic vaccines and therapeutic vaccines. Prophylactic HIV vaccines

² For further history of Institutional Review Boards, see R.J. Levine, 1988 (20).

have as their primary purpose the prevention of infection (although, in certain cases, the term is used for vaccines intended to prevent establishment of infection). Therapeutic HIV vaccines are given to persons who are already infected to slow, halt, or reverse the progression of disease. In this sense, therapeutic vaccines are similar to any other treatment.³ This chapter discusses ethical issues surrounding clinical trials of prophylactic HIV vaccines.

While the three phases to the testing of vaccines in human populations were described in detail in chapter 2, the focus of this chapter is on ethical issues related to the conduct of clinical efficacy (Phase III) trials of HIV vaccines, although many of these issues are also relevant to the conduct of Phase I and Phase II trials. The final portion of this chapter discusses some ethical issues related to the use of an approved HIV vaccine in clinical practice.

ETHICAL ISSUES IN THE DESIGN OF CLINICAL TRIALS

These are a number of ethical considerations in the design of a clinical trial of a prophylactic HIV vaccine. Fundamentally, a trial that is not designed to yield valid, scientifically new, or confirmatory results is unethical and should not be conducted because no burden or risk on the part of research participants is justified if some benefit is not likely to result. Assuming that there is scientific justification to proceed with a clinical trial, specific questions related to design must be addressed.

■ Is Randomization Ethical?

Benjamin Freedman argued that it is only ethical to randomly assign trial participants to an experimental intervention where there is “clinical equipoise”—“that is, where there is uncertainty in the medical or scientific community generally about whether the intervention is beneficial (10). This

does not require, however, that the investigators themselves not have a “treatment preference.”

Because HIV is such a serious condition and the consequences of erroneous vaccine research findings would be great, it may be less ethical to conduct a vaccine trial that does not randomly assign trial participants. Randomized clinical trials are not the only means of assessing effectiveness, but because they minimize the potential for bias, they are considered the “gold standard” for clinical research (30). Randomized trials of HIV vaccines are particularly important because factors that affect HIV transmission, such as risk behaviors or concurrent infection with other sexually transmitted diseases, have the potential to bias the results of an observational study of vaccine efficacy.

Once there is consensus that an HIV vaccine is protective, it would not be ethical to conduct a vaccine trial that randomly assigns research participants to a placebo vaccine.⁴ It is ethical to conduct randomized clinical trials to test hypotheses, but not to provide confirmatory data.

■ Will Trial Participants Receive Counseling About Risk Behaviors?

Any clinical trial of an HIV vaccine should include behavioral counseling about risks for HIV transmission at every study visit. This is ethically required, not only because the vaccine is unlikely to be completely efficacious and some participants in a randomized trial will not receive the vaccine, but also because there is a responsibility to provide trial participants with some benefit if possible at not too great an expense. Moreover, the provision of behavioral counseling reinforces the message to trial participants that vaccines are but one part of an overall strategy to prevent HIV transmission, which also includes the avoidance of behaviors that increase one’s risk of infection. This will also be an important message to convey

³ The possible uses for an HIV vaccine are described in chapter 2, box 2-1, “The Spectrum of Possible Strategies for Uses of HIV Vaccines.”

⁴ After an HIV vaccine is approved, new generation experimental vaccines would be tested against the approved vaccine.

when HIV vaccines are incorporated into clinical practice.

Although the power of a study to detect differences between vaccine and placebo recipients will be reduced if the recipients' baseline rate of seroconversion falls, ethically the most effective behavioral counseling should be provided to participants.

■ Are Procedures Adequate for the Confidential Handling of Research Data?

In research, it is imperative that all aspects of data collection, including recordkeeping, data storage, and the sharing of information be performed in a manner that maintains participants' confidentiality. Persons known or even suspected of being HIV positive have experienced discrimination in housing, employment, and insurance, as well as social discrimination from peers (14). Because the HIV-related information gathered in HIV vaccine trials is particularly sensitive, the maintenance of confidentiality in these trials is especially important.

Procedures should be established to maintain the confidentiality of trial participants. A number of practical measures should be taken. For example, participants should be assigned unique identification numbers, and all interactions with participants should be conducted using those unique identifiers (or first names if trial participants prefer), rather than the trial participants' full names. A "master key" that links participants' full names to their unique identification numbers should be kept in a locked cabinet or other secure place, and accessible by only a limited number of investigators.

The participants' full names should not be revealed to those who interview the participant, draw his or her blood, provide behavioral counseling, administer the vaccine, or otherwise personally interact with the participant. All written information and specimens should be labeled with the participants' unique identifiers, and these should be kept in locked storage units or computer files with controlled access. Most important, staff

at all levels should be trained in procedures for maintaining confidentiality.

Participants in clinical trials of HIV vaccines should be assured that they may have access to their files once the trial is completed. Participants should be provided with documentation of their participation in the HIV vaccine trial, as it may be needed later to demonstrate, for example, that vaccine is the source of a false-positive HIV screening test.

Some researchers have sought to bill participants' insurers for any trial-related procedures (e.g., laboratory analyses, screening tests, etc.). The primary legal reason why insurers rarely pay for these procedures is that insurance policies only provide reimbursement for "medically necessary" treatments. One's decision to participate in a clinical trial is completely discretionary and the efficacy of the preventive therapy or treatment is unproven, so the experimental therapy cannot be considered medically necessary. There is also an important ethical reason such claims should not be filed: the filing of claims would pose unjustifiable risk to trial participants' confidentiality. In HIV vaccine trials, the filing of a claim would require the disclosure of the participants' names and sensitive HIV-related information to individuals who have no relationship to the trial. The disclosure of sensitive HIV-related information may put the participants' access to future coverage at risk. Therefore, payment for trial-associated medical procedures should be the responsibility of the investigators and vaccine sponsors, and funds for these procedures should be included in the trial budget.

■ Is There Community Involvement in the Planning and Conduct of the Trial?

Although the importance of a community board is usually emphasized in discussions of clinical trials in developing countries, a community board is equally important for trials conducted in the United States or other developed countries. A community board often is comprised of approximately 10 persons, usually trial participants, who meet with the investigators periodically through-

out the course of the trial, beginning with its developmental stage. Community boards often review and make recommendations about how the trial should be conducted. In some settings, new staff must be interviewed and approved by the board before they are hired. The community board benefits both the trial participants and the investigators. Participants can contact board members, who may seem more accessible than investigators, with questions and concerns. The members of the board are intended to be representative of trial participants, and will help ensure that participants' rights are protected. Researchers are likely to benefit from participants' greater involvement and, perhaps, "ownership" of the research, that is engendered by the community board; this could result in greater retention and better adherence by participants to study protocols.

SELECTION OF SAMPLE

There are a number of ethical considerations in recruitment and selection of trial participants. Generally, individuals suitable for clinical efficacy (Phase III) trials are from populations with a high incidence of HIV infection, and should be from communities with sufficient willingness and infrastructure to support a trial (31). A candidate vaccine should be tested in the populations in which it would be used in clinical practice because a study's findings may not be generalizable to populations other than those from which the study sample was chosen.

■ Special Populations

Historically, a major thrust of research ethics has been the protection of vulnerable populations from enrollment in human subject research without their (or their guardians') knowledge or consent (an autonomy-based concern) or without justification for their specific inclusion (a justice-based concern) (25, 33). More recently,

concerns about not burdening any population disproportionately have been supplanted by concerns that there be fair access among populations to what may be the benefits of participation in research. In both cases, the key concern is one of justice: all populations have a right to the potential benefits of research, and no population, particularly those unable to provide voluntary consent, should bear the burdens of research unjustly.

"Vulnerable" populations, or those that may be unable to provide valid informed consent, can be divided into two general categories. First are those who have the mental capacity to consent, but, because of their situation, do not have the practical ability to provide consent *voluntarily*. Examples of this category of vulnerable populations include prisoners, women in certain societies, some desperately ill patients, or those in a dependent relationship with the investigator, such as medical students or patients. Second are those who are unable to consent by virtue of a characteristic or condition inherent to them. Examples include children and persons with mental illness or mental retardation who do not have the mental *capacity* to provide consent. The obligation to protect vulnerable participants, particularly in light of gross harms to which they have been submitted in the past,⁵ remains paramount. At the same time, all of these populations also have a claim to what may be considered the benefits of participating in a trial.

In determining whether to include any vulnerable population in research, two questions should be answered. First is whether it is necessary to include the vulnerable population to obtain knowledge that cannot be gained from studying other, less vulnerable populations. For example, one can only determine the efficacy of a drug or vaccine for children by conducting clinical trials involving children. Second, do the members of the vulnerable population (or their guardians) consider the research to be of benefit to themselves.

⁵ An initial expose of unethically conducted biomedical research was presented in a book by Beecher and colleagues in 1966 (4).

The question of whether to include pregnant women in clinical trials has been given particular attention in recent years (24). Until recently, pregnant women have largely been excluded from clinical trials because of concerns about risks to the fetus. However, the only way to study whether a vaccine prevents transmission of HIV from mother to fetus (vertical transmission) is to include infected pregnant women in clinical trials. As discussed in chapter 2, although pregnant women have been excluded from HIV vaccine trials in the past, there are now clinical trials of vaccines to interrupt vertical transmission that have enrolled infected pregnant women.

Certain populations at increased risk for HIV infection may be considered vulnerable, not because of a hampered ability to provide consent, but because they are at particular risk of social harms from trial participation. For example, some high-risk behaviors are illegal (e.g., injection drug use, prostitution, and, in certain jurisdictions, male-to-male sex). Members of these high-risk groups may increase the chance of detection as a result of trial participation. At the same time, such high-risk individuals are targeted for HIV vaccine clinical efficacy trials because they have high rates of seroconversion and because they offer an opportunity to study the interaction between the vaccine and specific risk behaviors. Investigators should assure these potential research participants that their confidentiality will be protected.⁶

■ Members of Racial and Ethnic Minority Groups

African American and Hispanic persons are likely to be recruited for HIV vaccine trials in greater proportion than their representation in the population, given that they are highly represented among groups at risk for HIV infection. There is reason to believe that African American and Hispanic persons are more likely to be suspicious of the intentions of investigators, given the history of abuses of members of racial minority groups in clinical research, most notably in the Tuskegee syphilis study (29). Involvement of community boards and “gatekeepers” is especially important from the outset of HIV vaccine trials to better ensure that trial participants’ needs are addressed and that investigators are sensitive to cultural concerns.

It is also important to ensure that members of racial minority groups are recruited for participation in research trials given that the prevalence of infection is higher among these groups and that many members of these groups would be candidates for a vaccine once approved.

INFORMED CONSENT

Rooted in the principle of respect for autonomy is an ethical obligation on the part of investigators to engage potential research participants in the process of informed consent and to obtain adequate consent from all participants.⁷ The U.S. Public

⁶ Investigators may want to obtain a Federal certificate of confidentiality to better ensure protections for this category of participants. Public Health Service Act, § 301(d), 42 U.S.C. The Act states that special protection will be granted “sparingly” to research projects of a “sensitive nature where the protection is judged necessary to achieve the research objectives.” 42 U.S.C. § 301(d). Examples of the types of research that may qualify are those that collect “information relating to sexual attitudes, preferences, or practices; alcohol, drugs, or other addictive products; illegal conduct; information that if released could reasonably be damaging to an individual’s financial standing, employability, or reputation; information that would be recorded normally in a patient’s medical record, and the disclosure of which could reasonably lead to social stigmatization or discrimination; information pertaining to an individual’s psychological well-being or mental health.” Researchers who have obtained a certificate of confidentiality “may not be compelled in any Federal, State, or other local civil, criminal, administrative, legislative or other proceedings to identify [research participants].”

⁷ See Beauchamp and Childress, 1989 (3), for further discussion of ethical principles.

Health Service established a policy in 1966 (revised substantially in 1974)⁸ that all federally funded research must be approved by external review boards that have as part of their responsibility ensuring that investigators obtain informed consent.⁹ Essentially all academic institutions require that all research involving human subjects (not just that funded by the federal government) secure such approval. The need for this external oversight arose from the recognition that there may be conflicts of interest among clinical investigators.

The process of informed consent for a clinical trial involves: 1) providing the prospective participant with information relevant to his or her decision about participation in the trial, 2) ensuring that the participant understands that information, 3) ensuring that the participant is choosing to participate voluntarily, and 4) documenting the consent of the participant.¹⁰

The following information should be provided to potential participants: an explanation that they are being asked to participate in research, not clinical care; a statement of purpose of the research; an explanation of why they were selected; a description of all procedures that they may undergo, including duration, location, and frequency of study visits; a description of the “foreseeable” risks and benefits (both to the participant and others); the alternatives to trial participation (or to the experimental therapy or intervention); a description of how confidentiality will be protected; a description of whether there will be compensation for injuries resulting from participation; a list of those

of who can be contacted for questions or problems; and a declaration that participants have the right both not to participate in the trial and to cease their participation at any time, and that by so doing, the receipt of medical care or other benefits will not be compromised.

In addition to these general requirements, there are considerations specifically for HIV vaccine trials. Any clinical efficacy trial examining HIV transmission will need to limit its sample to persons who are not HIV-infected. Therefore, all potential enrollees will first be screened for HIV infection. There needs to be an informed consent process for this testing that is distinct from the informed consent process for enrollment in the research trial. The usual procedures for pre- and post-test counseling must be adhered to. In addition, information should be provided to the potential enrollee that explains that a positive HIV test renders the potential subject ineligible for participation. Moreover, some means of referral for those found to be infected must be established.

Particular problems may arise from HIV testing, in that certain states require the names of all persons who test positive for HIV be reported to the state health department. If such name reporting is required in the state where the research is being conducted, this should be disclosed to potential trial participants and included in the consent form. If the investigators, however, have received an exemption from this requirement, then there is the concern that persons will volunteer for the trial just to receive a confidential HIV screening test,

⁸ 45 Code of Federal Regulations, §§ 46.101-46.509.

⁹ Institutional Review Boards (IRBs) are established by an institution conducting medical research to assess the legal, ethical, and scientific aspects of research on human subjects. IRB approval is required by the Department of Health and Human Services (DHHS) before proposals can receive federal funding. IRBs must review research protocols on a regular basis, but not less than once a year.

Federal regulations for human subjects research require both a generalized as well as specific informed consent for subjects to ensure that they understand the nature of the trial, the lack of any expected benefit, and the risks that are involved. 45 C.F.R. 46.101 (1993). Additional requirements apply to trials involving pregnant women and prisoners. The regulations are administered by the DHHS Office of Research Risks. Agencies and departments outside of DHHS are also required to adopt similar requirements. Although U.S. courts have not always relied on federal requirements to determine the standard for informed consent in clinical trials, failure to comply with these requirements could also give risk to a suit in tort.

¹⁰ For a much more detailed discussion of informed consent see, e.g., Faden and Beauchamp, 1986 (8); and Appelbaum, et al., 1987 (2).

but with no intention of ultimately participating in the trial.

Once potential trial participants are selected from a pool of eligible persons, they should be provided with specific information as part of the disclosure component of the informed consent process, and investigators must ensure that each potential participant understands this information:

1. *The meaning of incomplete efficacy.* Potential trial participants should be informed that the investigators have no assurance that the particular vaccine being tested will actually be effective in preventing HIV infection, and, even if the candidate vaccine is effective, it is not likely that it would be completely effective in preventing HIV infection. Trials participants should therefore avoid high-risk behaviors, as they would had they never received the vaccine.
2. *The meaning of a placebo and the meaning of randomization.* Potential participants in a randomized clinical trial should be informed that there is a chance that they will not receive the experimental vaccine, and they should be informed of the likelihood of that chance. In some trials, investigators are choosing to provide the control arm of studies with an alternative vaccine, such as Hepatitis B vaccine, rather than a placebo vaccine. If so, this should be disclosed to potential trial participants.

Various analogies have been used to explain the concept of random assignment, including the flipping of a coin or choosing marbles from a jar, depending on the number of experimental and control groups employed in the study. What is most important is that participants understand that they may not be assigned to the group(s) receiving the experimental vaccine, that this assignment is made by chance, that they will not be told if they have received the experimental vaccine until the study is completed, and that the persons administering the vaccine as well as most of the other research personnel will also not know to which group they have been assigned.

3. *The importance of not being tested outside of the study.* Potential participants should be informed that they must commit to not be tested for HIV outside of the trial since that could reveal whether they have received the experimental vaccine. Participants' knowledge of their assignment could bias the results of the trial by affecting the participants' risk behaviors, their reports of side effects, and so forth. Admittedly, many investigators have hesitated to warn potential participants to not obtain HIV testing outside of the study, fearing that this knowledge may increase the likelihood that participants would obtain such testing.

At the same time, participants should be told that if they need to know whether they have become infected with HIV, they may obtain HIV tests from the investigators. Investigators would use the appropriate tests to diagnose HIV infection, and would inform participants if they have become infected with HIV.

4. *That vaccine recipients testing positive on commonly used HIV screening tests may suffer social harms as a result.* Potential trial participants should be made aware that certain social harms may occur as a result of trial participation. Vaccinees may test positive on the ELISA (enzyme-linked immunosorbant assay) screening test, and other commonly used screening tests, which may result in problems in obtaining health or life insurance, employment, military service, or in travel to other countries. Participants should also be told that they will receive a document that certifies their participation in the vaccine trial and explains that they may test positive for that reason. More specific tests may be used to determine whether they are infected with the virus; if requested, these tests would be conducted at the investigators' expense.

Potential participants should be told that vaccination may increase the difficulty of diagnosing HIV infection. Standard ELISA screening tests cannot determine whether a vaccinee is HIV infected; more specific tests must be used.

5. *That other social or personal harms might result.* Others may assume that trial participants are members of groups at increased risk for HIV infection and social stigmatization could result. Some have suggested that social harms from trial participation be monitored, just as are biological adverse events. A board could be established to monitor and review social harms and decide if these harms to trial participants are sufficiently severe to warrant termination of the trial.
6. *That participation in this trial may make participants ineligible for other HIV vaccine trials.* Because multiple vaccinations may confound interpretation of results, trial participants that receive the experimental HIV vaccine may not be eligible for participation in trials of subsequent and trials of possibly more effective HIV vaccines.

Cause of the large amount of information that must be conveyed in the informed consent process, some investigators have chosen to give potential participants a written test of their understanding of this information. (Tests could also be administered orally to participants who cannot read.) This test would be completed upon enrollment and at each subsequent visit. A participant's continued participation in the trial could be made contingent on their successful completion of the test. Participants who do not "pass" the test would receive more education before the test is readministered.

Investigators and sponsors have an ethical obligation to ensure that there is an independent Data Safety and Monitoring Board (DSMB) to examine trial data at preestablished intervals for convincing evidence of either significant effective-

ness or unacceptable harm from the experimental vaccine requiring termination of the trial.

Investigators also have the ethical obligation throughout the trial to provide participants with any other information that may reasonably be expected to influence their willingness to participate, and to evaluate whether continued participation in the trial is in the participants' best interests. The ethical obligation of investigators goes beyond providing information to the DSMB; it also could include information that becomes available through the vaccine research of others, HIV research in other realms, such as behavioral research, or relevant changes in public policy, if this can reasonably be expected to influence participants' willingness to participate.

RESEARCH IN DEVELOPING COUNTRIES¹¹

It is not ethical for investigators or vaccine manufacturers to conduct trials in developing countries merely because it is less expensive or more convenient. To ignore the need for effective vaccines in developing countries, however, would be ethically unacceptable because HIV is an overwhelming problem in so many of these countries. Moreover, strains of HIV from different parts of the world vary, as do cofactors that influence transmission of infection and disease progression;¹² thus, findings from vaccine trials conducted in the United States or other developed countries, would not be generalizable to developing countries. For these reasons, it is appropriate to conduct HIV vaccine trials in developing countries that have a high incidence of HIV infection. Box 3-1 describes international guidelines for human subjects research.

¹¹ International guidelines for human subjects research developed by the World Health Organization (WHO) and the Council for International Organizations of Medical Science (CIOMS) are described in box 3-1. See also Lurie, et al., 1994 (23); Katongole-Mbidde, 1993 (16); and Lawrence, et al., 1993 (19).

¹² HIV is not a single, genetically homogenous virus, but exists in multiple strains, which differ among individuals from different regions, as well as among individuals from the same region (22). It has been estimated that isolates of HIV differ as much as forty percent in their envelope sequences (9), and that at least five major families or clades of HIV exist around the globe (12).

BOX 3-1: CIOMS Guidelines for Human Subjects Research

In 1993, the Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO), approved a revised set of guidelines for human subjects research (6) *The International Ethical Guidelines for Biomedical Research Involving Human Subjects* begins with a statement of general ethical principles, and includes 16 guidelines.

The Introduction to the guidelines notes that one of the reasons for the revision of the guidelines, initially promulgated in 1982, was the prospect of clinical trials of HIV vaccines and drugs for AIDS

Guideline 8 provides that, in conducting human subjects research in developing countries, investigators must ensure the following: that persons in developing countries will not ordinarily be revolved in research that may equally well be carried out in developed countries, that the research should be responsive to the health needs and priorities of the community in which the research is being conducted, that every effort should be made to secure the Informed consent of individual research participants, and that proposals for the research should be reviewed and approved by an ethical review committee.

Guideline 15 states that the agency that is initiating the research should submit the research protocol to ethical and scientific review according to the standards of the initiating country, and the ethical standards applied should be equal to those applied to research conducted in the initiating country The guideline also states that the appropriate authorities of the host country should assure themselves that the proposed research also meets the host country's own ethical requirements

Although the guidelines do not address liability for adverse reactions, guideline 13 states that participants who suffer physical injury as a result of their participation are entitled to equitable compensation the guideline does not define, however, what compensation is equitable The sponsor of the research whether it be a pharmaceutical company, a government, or an Institution, should agree to provide compensation before the human subjects research is initiated, and research participants should be informed that such compensation is available The guidelines also state that the ethical committee has the responsibility to determine what Injuries are compensable and by whom

SOURCE: R.E. Stein, Blicher & Stein, Washington, DC, "Selected Issues of AIDS Vaccine Liability, " unpublished contractor report prepared for the Office of Technology Assessment, U S Congress, Washington, DC, Sept. 30, 1994

Local representatives should be included in the preparation and conduct of the vaccine trial. Such involvement will enhance mutual respect, which is ethically linked to respect for autonomy. Moreover, from a practical perspective, inclusion of local representatives can help ensure the success of the trial. Local representatives can provide a conduit for information relevant to the logistical operations of the research, can enlist support for the research, and can provide outside investigators with a greater understanding of local customs and expectations. Involvement of a senior investigator from the local site is crucial, as is the involvement of other local scientists. To involve local scientists, outside investigators may need to provide them with further training.

■ Recruitment

Questions have been raised over whether it is ethically acceptable to recruit participants who have little control over their ability to contract HIV infection, such as women whose male partners refuse to wear condoms or are not forthcoming about their own HIV status. However, this is the context in which some vaccines would be administered if proven to be efficacious. For this reason, it is appropriate to include such populations, with a commitment to trying to encourage these persons to protect themselves. It has been argued that it would be unethical to recruit participants from a community that denies the existence of HIV infection (16, 23, 27). Recruitment of these partici-

pants would be ethically acceptable only if targeted education were provided as part of recruitment.

■ Informed Consent

The issue of how to obtain valid informed consent in developing countries is paramount.¹³ Many of the issues that arise are the same as when obtaining consent in developed countries and many are not unique to HIV trials. Those that are special will be given attention here.

Ethics requires that both local and Western standards of informed consent be followed. Although there are debates about whether there exists “ethical universalism” (one set of principles that applies everywhere) or “ethical pluralism” (different principles in different contexts of cultures) (21), societies have different rules about who may grant permission for participation in research. In some societies, permission must be granted by a community leader or by someone other than the research participant (e.g., a woman’s husband). Ethics requires that all local customs and requirements be met out of respect for both the community and the individuals involved; however, this does not abrogate the obligation of the investigator to seek and obtain consent from the potential trial participant as well. Although some may consider this latter obligation to be ethnocentric on the part of Westerners, this remains the ethical standard for international research (6).

Potential trial participants should have an adequate understanding of the study and its components in order for informed consent to be valid. If the potential trial participants are illiterate, this would alter the means by which informed consent is obtained. Information would need to be provided in the local language or dialect and read to potential participants rather than conveyed in written form. Visual aids or diagrams might be included among the materials given to the potential

participants. Similarly, if some sort of a “test” of understanding is required, this would need to be conducted orally.

A more difficult situation occurs if the broad understanding of disease causation is completely different from Western understandings (1). For valid informed consent, it is not necessary for potential participants and investigators to have a completely shared understanding of disease causation. If the differences mean that, by virtue of participating, harmful consequences are likely to ensue, however, these persons cannot ethically be enrolled. Differences in beliefs must be evaluated on a case-by-case basis, and balanced with the need to ensure that any potential benefits of research participation not be denied to such populations.

Developing countries may not have the sophisticated tests necessary to detect HIV infection in vaccinees. Outside investigators should provide support, including these specific tests and necessary technical assistance. Investigators should also assist participants in securing documentation that they were enrolled in a vaccine trial. Although most vaccinees from developing countries would not have use for such documentation, it may be helpful in certain contexts, such as for immigration.

■ Other Responsibilities of Investigators

Investigators have the ethical obligation to not interfere with other prevention or public health efforts and not to draw the necessary number of local, trained health care personnel away from other important responsibilities. It also may be necessary to provide training to local personnel.

Once the vaccine is marketed, justice obligates the researchers and vaccine sponsors to make vaccine available to the community in which the trial was conducted. In developing countries, the obligation to ensure access to the benefits of vaccine

¹³ See Council for International Organizations of Medical Sciences and World Health Organization, 1993 (6). See box 3-1.

research would require the manufacturer to provide the vaccine for free or at cost.

COMPENSATION FOR ADVERSE REACTIONS

Although there may be no *legal* obligation to provide compensation for injuries incurred through research, it is generally agreed that there is an *ethical* obligation to do so (6, 18). Moreover, it need not be demonstrated that there was negligence on the part of researchers, but simply that harm resulted that would not have occurred had the person not participated in the trial. If compensation will not be provided, this should be explained in the informed consent process and included as part of the informed consent statement. Compensation need not be provided for harms that are not a direct result of research participation, such as for HIV infections not caused by the vaccine. Compensation decisions should be guided by the laws of the country in which the trial is occurring (17).

Potential trial participants should be informed that, even if investigators plan to provide compensation for harms resulting from trial participation, compensation will not be provided for harms resulting from the vaccine being less than completely effective in preventing HIV infection.

INCORPORATION INTO CLINICAL PRACTICE

A number of important ethical issues arise when a vaccine is approved and is used in clinical practice.

■ Efficacy

HIV vaccines are unlikely to be completely effective or efficacious. (The efficacy of licensed vaccines for other serious diseases ranges from 50 to 95 percent). Persons who believe that they are protected against infection because of the vaccine may be more likely to engage in high-risk behaviors. Further research is needed about the magnitude of this change in risk behaviors, and whether this outweighs the benefits of a partially effective vaccine. The public will need to be educated about

the partial nature of protection from an HIV vaccine.

One model of HIV vaccine efficacy concluded that “earlier use of a 60 percent effective vaccine would prevent more new HIV infections than later use of a more efficacious vaccine” (7). Nonetheless, this model considered the theoretical efficacy of vaccines, rather than their effectiveness in actual populations whose risk-taking behaviors may increase in response to vaccination, affecting the incidence of infection.

■ Informed Consent in Clinical Practice

The informed consent process in clinical practice is less rigorous than that applied in research. Although the law requires that clinical trials be approved by external review boards and that research participants sign detailed written informed consent forms, there are no similar legal requirements for informed consent in clinical practice.

In clinical practice, written informed consent is only required for certain types of medical interventions, typically surgery and nonroutine medical procedures. Public health interventions in particular have an extremely limited tradition of informed consent (although one exception is the informed consent process for HIV testing). Generally, American common law requires that the patient be given sufficient information upon which to make “an intelligent and informed choice” (32). Case law does not provide clear guidance, however, about the requirement for an “intelligent and informed” choice. Some courts have concluded that all information must be provided to participants, and others have found that information that a “reasonable” person would consider to be relevant must be provided. Negligence typically is based on a breach of the standard of care, and a tradition of rigorous informed consent is not part of the standard of care in clinical practice.

This is not to say that most clinicians fail to ensure that each patient has an adequate level of understanding before consent to medical interventions is obtained. However, the lack of standardization and regulation of informed con-

sent means that the extent to which this happens is unknown.

For HIV vaccines the consequences of an inadequate informed consent process may be severe. For consent to vaccination to be adequate, patients will need to understand that the vaccine is not completely effective and that they should continue to practice protective behaviors. Patients would also need to know the consequences of their testing positive on standard HIV screening tests. They also will need to be aware of the potential social harms from vaccination, particularly since vulnerable and “at risk” groups may be targeted for the first rounds of immunization. The risk of breach of confidentiality is greater in clinical practice, because outside parties (such as insurance companies) have access to medical records. Lapses in confidentiality would increase the potential for social harms to vaccinees.

CONCLUSION

Scientific progress is occurring in the development of HIV vaccines and some vaccines have entered clinical trials. Clinical testing of vaccines should not move forward, however, without the incorporation of appropriate ethical standards. A lack of attention to ethical principles not only would be morally reprehensible, but would lead to less effective research and compromised clinical findings.

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