UNAIDS Sponsored Regional Workshops to Discuss Ethical Issues in Preventive HIV Vaccine Trials

UNAIDS Report

Joint United Nations Programme on HIV/AIDS

UNAIDS

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UNAIDS/00.036 E (English original) September 2000

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UNAIDS-Sponsored Regional Workshops to Discuss Ethical Issues in Preventive HIV Vaccine Trials

UNAIDS
Geneva, Switzerland, 2000

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Introduction

Purpose of the Workshops

In September 1997, UNAIDS convened a meeting of experts in ethics, vaccine research, and social sciences in Geneva to discuss the ethical issues arising from the anticipated conduct of HIV vaccine trials in developing countries. It was apparent that this area of research had begun to highlight ethical dilemmas requiring special attention, and that a better understanding of these issues might facilitate the progress of HIV vaccine trials.

This meeting resulted in the identification of specific areas in which further discussion was deemed necessary, and the participants recognized the importance of these discussions occurring at the regional level. In addition, three background documents were written to further expand on the ethical theory underlying the issues that were identified.

The three regional workshops were organized to facilitate discussion on the ethical issues surrounding preventive HIV vaccine research. The outcome of these discussions is reported here, and was used to formulate a draft guidance document on ethics in HIV vaccine research. This draft document was discussed further at a meeting in Geneva on 24-26 June 1998, which included, among others, representatives of each of the regional workshops. In addition, this meeting addressed possible revisions and additions to current international guidelines on biomedical research, and recommendations for future involvement of UNAIDS in HIV vaccine research.

Participants

Participants were invited by both UNAIDS and the regional planning committees. In each region, the majority of participants was from the country which hosted the meeting, and a minority represented other countries in the region. Countries in the region surrounding the hosting country were represented by a single participant. Regional participants included lawyers, activists, social scientists, ethicists, vaccine scientists, epidemiologists, people working in nongovernmental organizations (NGOs), people living with HIV/AIDS, and people working in health policy. Each meeting included two individuals involved in vaccine trial advocacy in the United States. In addition, there were three to six members of the secretariat, some of whom varied between workshops. This included an expert in ethics, a vaccine scientist, and a rapporteur. The same rapporteur reported each of the three workshops.

In Brazil, 20 participants attended the workshop, in addition to three members of the UNAIDS secretariat. The majority was based in Brazil, with representation from Cuba, Barbados, Honduras, Trinidad, and the United States.

In Thailand, 17 participants attended the workshop, in addition to six members of the UNAIDS secretariat. The majority was based in Thailand, with one participant each from Australia, Cambodia, China, India, the Philippines, and Viet Nam, and two from the United States of America.

In Uganda, 16 participants attended the workshop, in addition to four members of the UNAIDS secretariat. The majority was based in Uganda, with one participant each from Ethiopia, Senegal, South Africa, and Zambia. In addition, at this workshop there was one participant from the National Institutes of Health in the United States.

Workshop Methodology

Workshop participants did not receive the workshop materials in advance, and thus were introduced to the issues on the first day of sessions. Each workshop began with a half day of background presentations and open discussion on the basic science of preventive HIV vaccines, principles of conducting clinical trials, ethical analysis in biomedical research, and community involvement in design and conduct of research.

The remainder of the three-day workshop was dedicated to intensive discourse on the ethical issues arising from the possible conduct of preventive HIV vaccine trials in developing countries. The tool that was used to guide these discussions was a hypothetical research proposal for a phase III preventive HIV vaccine efficacy trial, accompanied by study questions to assist in focusing the discussion on specific issues. The participants were divided into three small groups of approximately equal size. In Brazil, this division was based on language preference, and one group was conducted in Portuguese, one in Spanish and one in English. In the other regions, all groups worked in English. In all cases, groups were pre-assigned with an attempt to ensure a mix of regional representation and professional expertise. None of the participants of the regional workshops was made aware of the outcomes of previous workshops prior to discussions.

An attempt was made for all of the discussion groups to cover all of the topics included in the scenario (although in practice, time did not always allow for this). For each topical area, the small group discussion was followed by a plenary session, where the small groups reported on major issues covered, and where the items were opened to discussion by all participants. An attempt was made to identify opinion on which the entire group could agree, and to identify where there remained disagreement when the discussion was closed.

On completing the workshop, a draft summary was reviewed in a final plenary session by the entire group, and was extensively modified through further discussion in order to ensure adequate representation of the group's conclusions. In Brazil, the draft summary, which was reviewed by the group, consisted of brief consensus statements and outlined areas of conflict. By contrast, in the other two regions the draft summary consisted of a nearly complete report (the final items discussed on the day of the review were not included in the report that the group reviewed). The draft was modified according to group input, and then reviewed by members of the UNAIDS secretariat who were present at the specific workshop. The author of this final document and all of the draft documents also served as rapporteur for all of the regional workshops.

Finally, evaluation questionnaires were distributed to the group in order to assess the effectiveness of the workshop.

Reading this Report

The preliminary background discussions on ethics, science and community as they pertain to HIV vaccine research are not summarized here. Only the outcomes of the group discussions on the specific ethical issues are reported. In addition, language and terminology used to describe similar concepts often differs between regional reports. This is a reflection of the suggestions that came from participants in each region for how a concept should be described.

The intent of this report is to accurately reflect the discussion and conclusions that arose from each of the plenary sessions. It is important to note that the discussions that arose were facilitated by a specific case scenario (included in Annex 1) and questions related to this scenario. However, this

report describes generalized concepts, opinions, and principles that came out of the discussions, in a manner that might be applied to any form of HIV vaccine research. Some participants expressed concern that this process of generalization from a specific case to broader statements may not be valid for some of the topics, and that other specific cases may have given rise to different ethical principles being described.

For this report, an attempt was made to condense the plenary discussions into topical areas. These topical areas do not necessarily coincide with the numerical divisions made in the study questions. Within each topical area, the level at which consensus was reached is identified by the title consensus. There were no votes taken on these issues, and consensus here does not necessarily reflect unanimity, but rather a general sense of agreement without major resistance from any participants. Where there was significant disagreement or controversy on a topical area, this is identified by the title "Controversy". Finally, where there was general discussion that added detail to the consensus statement, or describes specific regional experiences, this is identified by the title discussion.

Summary

The outcomes of the three regional workshops were very different on some topics and similar on others. The following is a brief outline of issues on which the three regions held similar perspectives and those on which they did not.

Vulnerability to Harm or Exploitation: The current terminology of 'developed' and 'developing' is not adequate for comparing the characteristics of a population, community or country which lead to vulnerability in relation to vaccine trials. Rather, there are specific conditions that contribute to vulnerability that should be recognized and addressed in these discussions. These were defined, with minor differences, by the three regions.

Collaboration in Phase I, II and III Trials: There was agreement that repeating phase I and II trials in a host country that have already been conducted in a sponsor country is useful for familiarizing the public, government, and scientific community and for building capacity. However, there was disagreement among regions on whether phase I and II trials should be conducted in a host country if they were not already completed in the sponsor country. There was also disagreement as to whether it is always necessary to repeat a phase I and II trial in a host country that has already been completed in a sponsor country, and whether it is always necessary to conduct a phase III trial in the sponsor country prior to or simultaneously with conducting a phase III trial in the host country.

Scientific and Ethical Review Process: There were some differences in how each region thought this should be conducted. However, there was agreement that scientific and ethical review capacity must both be available and effective in the host country before an HIV vaccine trial is considered. There was also agreement that this is an area where international organizations such as UNAIDS have an important role to play. This role was defined by all groups as including capacity-building, but by some groups also as including conducting a complementary ethical review of trials and providing guidelines for representation on ethical review committees. Other issues discussed included how to ensure independence of the review process, what would constitute appropriate ethical review in the sponsor country, how capacity can be built, and the role of the community and government.

Community: Members of the community (including at a minimum the people who are likely to participate in trials, but usually also other groups) should be part of the process of development, approval and conduct of HIV vaccine trials. Defining 'community', mechanisms for ensuring active participation and approaches to addressing disagreement within a community were discussed.

Control Arm in Trials: The use of a substance in the control arm of an HIV vaccine trial that is not active in preventing HIV is ethical as long as an effective vaccine is not known. However, there was not agreement on whether a vaccine that is known to be effective against another disease should be offered to participants, nor what level of effectiveness of a proven HIV vaccine would warrant that it be used in a control arm.

Informed Consent: Individual informed consent is required for all HIV vaccine trials. However, it was acknowledged that this is often difficult to accomplish, and many problems specific to the regions were described, with some potential solutions being offered.

Special Populations: Women of childbearing age, pregnant women, children, and persons with mental disabilities were discussed. There was a variety of opinions on these issues, both within and between regions, and in most cases there was not agreement. Controversy arose over whether paternalism on the part of the scientific community is justified; whether individuals should have the right to decide for themselves to participate in trials or not, given the data available; and whether the 'traditional' approach of excluding some of these groups places them at an unreasonable disadvantage because data on vaccine effectiveness and access to the vaccine will be delayed.

Counselling: Participants in an HIV vaccine trial must have access to high-quality risk-behaviour counselling and to condoms and syringes. There was discussion and some difference of opinion on what this counselling should include, what 'standard' should be applied, how to ensure quality and how to ensure independence from the investigators. However, there was agreement that counselling should never be compromised in any country.

Treatment and Care: The regions differed widely between one another on whether participants who become infected during the course of a trial should be provided with HIV treatment if it is not generally available in the host country. However, on this issue, there was generally agreement within each of the regions. One region felt that treatment should be available at the level of the sponsor country, another that it should be available at the level of the host country, and the third took a position somewhere between these two.

Undue Inducement and Coercion: This was discussed only briefly in most regions. It arose in the context of providing a known public health vaccine to participants in the control arm of a trial, and in the context of providing treatment to those who become infected in the trial. Opinion differed widely on the significance of undue inducement in HIV vaccine trials.

Compensation: Regions varied on the aspects of compensation for harm that were discussed.

Intellectual Property: The contribution of host countries to the success of HIV vaccine trials is substantial, and thus requires that discussion on claim to intellectual property for a specific trial be carried out prior to the trial and be specified in the contract. There was discussion on who in a host country might have claim to intellectual property and how negotiation of intellectual property could be combined with negotiation of other benefits to the host country that might arise from discovery of an effective product.

Access to Vaccine: All regions agreed that historical examples of 'developing country' participation in vaccine research where access to the final product has not occurred must not be repeated in HIV vaccine research. Effective vaccine must be free and available at least to those who participated in the trial and to other high-risk groups in the host country. Potentially, the product should also be available to other developing countries. It was agreed that a discussion on availability should take place prior to the trial beginning, but it was not agreed what level of assurance, and what level of detail should or could be included in the agreement prior to knowing results of the trial.

Workshop Reports

Ouro Preto, Brazil, 1-3 April, 1998

1. Vulnerability to Harm or Exploitation

Consensus:
Rather than using the terms 'developed' or 'developing' countries or communities, it would be better to consider certain characteristics that identify countries or communities which may be vulnerable to harm or exploitation from scientific research (specifically HIV vaccine trials). The characteristics of a vulnerable country/community should include some or all of the following:

- Limited economic development (such as is reflected in the human development index of the United Nations Development Programme (UNDP)).
- Inadequate protection of human rights, and discrimination on the basis of HIV antibody status.
- Inadequate community/cultural experience with, or understanding of, scientific research.
- Limited political awareness of the importance and process of vaccine research.
- Limited availability of health care and treatment options.
- Limited ability of individuals in the community to provide informed consent.
- Insufficient formal experience or capability within the host country to conduct ethical and scientific review of proposed research.

2. Collaboration in Phase I/II (Safety and Immunogenicity) Trials

Consensus:
Phase I/II (safety and immunogenicity) trials that have been conducted in a 'developed' country should be repeated in a 'developing' host country before proceeding to a phase III (efficacy) trial in the host country. These phase I/II trials could be conducted with candidate vaccines adapted to locally prevalent HIV subtypes.

Discussion:
Taking this step helps to build ethical and scientific review capability within the host country before a large efficacy trial is conducted.
These trials serve to educate the population, the government, and the scientific community, which all must be active and informed participants in order for an efficacy trial to be successful. Anecdotal mention was made of countries in which scientific research is not understood or accepted, and where suspicion of the intent of the sponsor may be so great as to make a phase III trial impossible. Lack of understanding in these countries is in part a result of being in a position of receiving the final products of scientific research, and seldom being involved in the research and development phase.
There is a scientific rationale for conducting phase I/II trials in the host country, since the human genetic, nutritional, and environmental characteristics may differ enough between sponsor and host countries to significantly affect safety and immunogenicity profiles of the vaccine. These phase I/II trials could be conducted with candidate vaccines adapted to locally prevalent HIV subtypes.

3. Phase III (efficacy) Trials

Consensus:
A phase III trial may ethically be conducted in a 'developing' country without being conducted simultaneously in a 'developed' country.

Discussion:
If strong opposition to undertaking the trial exists in the 'developing' country, this practical consideration may preclude moving forward. The example of one country in the region was described, in which it was believed that the public would be suspicious of the motive of any trial that had not already been, or was not in the process of being, conducted in a developed country.

4. Review of Vaccine Trials

Consensus:
Decisions regarding which candidate vaccine is appropriate for study in human subjects in the host country require adequate scientific expertise, but very early in the process of formal negotiation, should also involve government, the community affected by HIV/AIDS, and other bodies or players deemed appropriate under the circumstances of the host country. In order to proceed with a phase I, II or III vaccine trial in a 'developing' country, there should be evaluation and approval of the proposed research by scientific, ethical, and community review bodies from within the host country.

Discussion:
Many countries do not have effective mechanisms in place for ethical or scientific review of proposed scientific research. The host country should develop the organizations and procedures for ethical and scientific review, with assistance from non-partisan, independent agencies such as UNAIDS. These structures may have been developed previously for consideration of earlier studies, or may be developed specifically for approval of an HIV vaccine trial. In any case, they should be capable of operating effectively prior to consideration of any HIV vaccine trial.
Capacity-building is part of the process of development and skills transfer, and part of a responsibility the sponsor has to contribute to improved conditions in the host country.

5. Candidate Vaccine Choice

Consensus:
The same scientific criteria that are used to identify an appropriate candidate vaccine for a 'developed' country should be applied to the choice of a candidate vaccine for a 'developing' country.

Discussion:
There is not consensus within the scientific community at this time regarding what degree and what components of immunogenicity, what viral subtype specificity and what genetic, nutritional, and environmental factors are important in predicting the likelihood of a candidate vaccine being effective. However, there was consensus within the group that the best available opinion on this matter should guide the choice of candidate vaccines for phase III trials in developing countries. The criteria applied to 'developing' populations should be the same as those applied to 'developed' populations.

Controversy:
Because criteria for a promising candidate vaccine are not clear, a final decision on whether to conduct a phase III trial must include appropriate local scientific, ethical, and community evaluation. However, there was not agreement within the group about whether a candidate vaccine for which there is not consensus within the scientific community should proceed to a phase III trial even if the host country approves it.

6. Community

Consensus:
Disagreement within the scientific/medical community, the HIV-affected community, and government concerning the appropriateness of scientific research is common. However, work on informing and developing consensus within these sectors must be carried out rigorously.

Discussion:
There was extensive comment on the difficulty in defining community, deciding what community is most important to consult with and choosing appropriate key informants. However, no concrete suggestions were made on how to address this issue.

When there is lack of consensus within a particular community, it is often due to inadequate information, and the process of education of the relevant sectors should be a major part of consensus-building.

Controversy:
There was debate concerning who should be able to veto a trial (scientists, community, government, and sponsor), or decide to continue in spite of lack of consensus.

Some believe that effective individual informed consent will provide adequate protection when there are issues that cannot be agreed upon by scientists, ethicists, and community advisory boards. However, some do not agree that the decision should be left to the individual if there is significant disagreement at the level of these planning groups.

7. Intellectual Property

Consensus:
A discussion about intellectual property needs to take place early in the process of proposal development. It may be reasonable for the host country to claim a right to intellectual property if its participation in the trial is deemed essential for the development of the particular candidate vaccine.

Discussion:
Intellectual property may become an important commodity in the negotiation of vaccine availability to the host country following the trial. However, access to a successful vaccine following the trial should be dealt with separately from the question of who has the right to intellectual property.

Controversy:
It is not clear who in the host country (investigators, government, and population) should have a claim to the intellectual property rights, though a majority was of the opinion that this should not be the exclusive property of the investigators.

8. Control Arm in Trials

Consensus:
A study design that is not anticipated to have a good chance of providing conclusive results is not ethical. Controlled trials for preventive HIV vaccines, with an active arm (the candidate HIV vaccine) and a control arm (which could be an inactive placebo or, better, an unrelated vaccine) are currently the most appropriate from both a scientific and ethical point of view. Providing a vaccine known to be effective in preventing a disease other than HIV (such as hepatitis B) to those in the control arm of the trial would address issues of justice and beneficence for volunteers. However, the use of inactive placebo is not perceived as inflicting greater harm than the use of an active HIV vaccine, since there is currently no preventive HIV vaccine with any proven level of effectiveness.

Discussion:
Participants in a control arm should be guaranteed of receiving the vaccine should it be found effective at completion of the trial.
If a non-HIV vaccine were to be offered to those in the control arm, or to other participants, it would be necessary to choose one that is appropriate for that particular population. For example, it might not be appropriate to use a hepatitis B vaccine in a population that already has significant prevalence of immunity to hepatitis B.
It is important to consider alternative study designs that could provide the required information subjecting the fewest number of individuals to a placebo. Suggestions included a sequential model, involving an efficacy trial of intermediate size, and multi-arm trials with only one control group and several active arms.

9. Informed Consent

Consensus:
Nothing can substitute for individual informed consent. It is not ethical to conduct a trial involving groups or individuals in which there are significant problems in obtaining it. When obtaining individual informed consent is difficult, a sponsor might consider initiating activities that will aid the individuals, the population or the culture to develop the capability to give individual informed consent. There was discussion concerning several groups that are uniquely vulnerable, and these issues are outlined below.

Discussion:
It was pointed out that in some countries/cultures the concept of a woman giving consent independently of a man is not possible.
In situations where a community leader must consent prior to individuals within the community, the leader's consent should not substitute for individual consent.
Mental incapacity of different forms could create a situation in which an individual is not capable of consenting to participate in research. Though there may be a rationale for attempting to enrol these

individuals in a vaccine trial due to risk of being infected, it would be preferable to provide a proven vaccine to this group following trial completion.
After reaching the age of legal majority, adolescents may give consent to participate in vaccine trials. However, there was controversy surrounding the enrolment of adolescents prior to the age of legal majority.
It was suggested that neonates may be an appropriate group to enrol in a preventive HIV vaccine trial to prevent vertical transmission, and this would require consent of the parent.
Safety data in children and neonates would be required before administering a vaccine in a phase III trial to these age groups.

Controversy:
Adolescents who have not reached the age of legal majority but are at risk of acquiring HIV constitute a difficult category. The group did not agree on whether this category should be invited to enrol through parental permission; whether they should give their own informed consent; or whether they should be excluded as a group from participating in a vaccine trial until efficacy has been proven in phase III trials in adults. The possibility of enrolling in a phase IIIb or phase IV trial was suggested.

10. Gender, Pregnancy and Breast-Feeding

Consensus:
Women of childbearing potential should be enrolled in preventive HIV vaccine trials. Animal data on teratogenicity would have to be available before considering enrolling pregnant women, or allowing women who become pregnant while participating in the trial to continue.

Controversy:
Should women who are pregnant or breast-feeding be invited to participate? This issue raised significant debate. A majority was of the opinion that paternalism is justified for protection of the fœtus. A minority was of the opinion that a woman has the right to make an independent, informed decision for herself and her fœtus. There was disagreement on what level of evidence of vaccine safety in pregnancy is adequate before pregnant women may be permitted to make individual decisions about participating, through individual informed consent.

11. Counselling, Treatment and Care

Consensus:
Preventive risk behaviour counselling, general HIV care and treatment, post-exposure prophylaxis and antiretroviral therapy (whether early or late) were all considered to be subject to the same ethical imperative; that is, all should be provided to trial participants according to the best scientific evidence for effectiveness available at the time of the trial. There was a strong sense of consensus on this issue.

Discussion:
This was perceived by the group as the most important topic to be discussed during the workshop, and the most likely to affect the progress of HIV vaccine trials.

It would not be ethical to deny counselling, post-exposure prophylaxis or antiretroviral or other treatment to participants solely for the purpose of making a vaccine trial more valid or statistically powerful.

Local capacity for counselling must exist or be developed, be flexible and multi-cultural, involve information and methodology at an appropriate level, and include distribution of condoms and needles. (However, it was also pointed out that in some countries, needle exchange is illegal.)

Post-exposure prophylaxis should be provided if it has come into common use in the host country. It was acknowledged that evidence that supports the effectiveness of post-exposure prophylaxis outside of the occupational setting is currently very limited.

Treatment for those who become infected should be provided at the level of that offered in the sponsoring country. It should continue at least for the duration of the trial, and further provision should be negotiated. This would include early antiretroviral treatment in the case where it is proven to be effective.

There should be a disease management or research protocol that all who seroconvert during the trial would enter.

It was acknowledged that making antiretroviral medication available in a study setting would be very expensive, but also that little research or effort has been dedicated thus far to developing creative economic mechanisms for providing this.

The need to measure secondary endpoints was not perceived as a valid rationale for withholding early treatment if treatment was proven to be effective. In addition, it was not generally held that providing early treatment would necessarily preclude an analysis of vaccine effectiveness. There was discussion about the likely proportion of participants that would realistically be diagnosed during early infection, and would choose to accept early therapy. It was suggested that those who do not receive early treatment due to choice or circumstance may still contribute substantial data on which to base an analysis of effectiveness.

A test that is capable of distinguishing HIV infection from vaccine-induced antibody response would need to be made available to all participants by the sponsor.

Controversy:

Significant conflict arose in defining the appropriate measure by which to determine what level of treatment or prevention should be provided in a developing country research setting. There was agreement that scientific evidence for effectiveness of treatment or prevention interventions gives the most important guidance for what should be provided. There was also agreement that there should not be a compromise made solely because of limited resources in the host country. However, it was acknowledged that, in many cases, common treatment practice in 'developed' or 'developing' countries is not based on scientific evidence, but on prevailing opinion, or political or cultural persuasion. Terms such as 'best proven', 'best possible', 'standard of care', 'highest attainable' and 'policy' were considered, but each was found to have its own limitation. For example, there was a sense of mistrust when using the term 'highest attainable', since 'attainable' is not an absolute, but is a function of priorities and decisions related to resource allocation. Who makes these decisions, and how they are made, have a great impact on the final outcome. This issue of defining the most appropriate measure was left unresolved.

Is this principle of providing what is 'best proven' to those participating in the trial open to any qualification? To this a minority reluctantly answered that there may be exceptions to providing the 'best proven' care, but that this was something that could only be determined in the local context, through the deliberation of an empowered and informed community.

12. Access and Availability of Vaccine

Consensus:
Availability of a vaccine following a phase III trial must be ensured. This should include a statement of intent prior to conducting the study, but it is recognized that details of how availability might be ensured will need to be worked out on completion of the trial. In any case, it must be clear from the outset that the likelihood of the vaccine being available to the host country at trial completion is high.

Discussion:
The appropriate target groups within the host country, based on epidemiological data (identifying highest preventive impact of vaccination) are entitled to the vaccine once the trial is finished. The country that takes the risk should benefit first, and a plan for access must be discussed prior to beginning the trial. The second priority is that all the other developing countries in the world who are involved in vaccine trials have access (as a matter of distributive justice), and the third is all other countries in the world.
Consideration should be given to an increased cost to 'developed' countries to subsidize the cost to 'developing' countries. However, it was pointed out that differential pricing is not an appealing strategy for some pharmaceutical companies.
There was little controversy on this point, and all agreed that in order to fulfil principles of justice, those who are involved in the trial must benefit from a successful vaccine.
Access issues and mechanisms are not being dealt with adequately at this time.

13. Items Not Discussed

Lack of time prevented the Brazil group from dealing with several issues that were covered by the discussion questions. These included:

What level of compensation for harm or injury as a result of participation in research should be provided, and for whom?

What level of benefit to study participants would constitute an unreasonable inducement to volunteer for the study (e.g. providing post-exposure prophylaxis and physician care)?

What unique issues arise in the context of trials involving live-attenuated vaccines?

Bangkok, Thailand, 20-22 April, 1998

1. Collaboration in Phase I, II and III Trials

Consensus:
It is preferable that phase I/II (safety and immunogenicity) trials be repeated in a host country prior to phase III trials. (It is necessary to conduct phase I/II trials in the sponsor country first, unless the candidate vaccine is subtype-specific for the host country.) There is not an ethical imperative that phase III trials be conducted in a developed country prior to or simultaneously with phase III trials in developing countries. Conducting a phase I/II trial in the host country has scientific merit in that a different population with different genetic, nutritional, and environmental attributes may respond differently to the candidate vaccine. In addition, the viral subtypes prevalent in the host country may be different.

Discussion:

Phase I/II trials also allow for education of the public, the government and the media about scientific research and vaccine trials, building technical capability and improving decision-making ability, which will facilitate conduct of a phase III trial in the future.
Some countries (e.g. China) have a law that there must be phase I /II trials in the country before phase III.
The 'capacity building' that results from conducting phase I/II trials even in developed countries does not usually target the same groups that are likely to be involved in phase III trials, and thus the development that results does not always benefit the appropriate community.
It is important not to let the urgency of the epidemic push forward research that may not be appropriate scientifically, or that a country or community is not prepared for.
Some participants felt that if there was no clear scientific or capacity-building advantage to conducting phase I/II trials in a developing country, then these are not necessary.
Conducting a phase III trial only in a developing country is not necessarily unethical, but would require an explanation from the investigators as to why this is occurring.
One group suggested that the criteria that help to define 'developing country' in the context of vaccine trials are technical and political. Specifically, the degree of protection of human rights, the ability of individuals to give informed consent, and the development of the ability to conduct scientific and ethical review were raised as considerations when attempting to determine whether a country or community be considered 'developed' or 'developing'. This was not discussed in depth by the large group.

Controversy:
Some participants were concerned that conducting phase I/II trials in a host country might occur primarily for the purpose of developing capacity (scientific expertise and infrastructure, scientific, and ethical review bodies). It was suggested that the capacity-building is necessary, but that it should be furthered by other mechanisms, preferably prior to the introduction of trials, and that scientific research should be driven by the scientific question rather than by the need for capacity. There was not agreement on this issue.

2. Community

Consensus:
It is important for the community to be involved in development and conduct of preventive HIV vaccine studies. Involvement of the community should not be considered a consultation, but rather a two-way interaction between equal parties that effectively becomes part of the decision-making process.

Discussion:
The difficulty in defining the community that should be involved was discussed. There was agreement that persons living with HIV/AIDS can contribute an important perspective since they bring a high level of awareness of some of the important issues to the discussion. However, they are not the people who will be participating in these trials. Groups that are likely to be involved in trials, such as commercial sex workers and drug users, are less likely to be well organized and prepared to contribute to the research development process. There is a need to involve leaders and spokespersons from these groups, as well as representatives from NGOs that have an understanding of these groups. Involving media should also be considered.
Attempting to define a community was identified as an important issue, but was not discussed in depth; concepts such as shared customs, traditions, and authority structures were offered.
If there is disagreement between community representatives and researchers concerning the study protocol, then further work to develop consensus is required before the study proceeds.
In some cases, it may be preferable that a public forum occurs rather than relying only on community representatives.
In some countries, there is experience with communities being involved in the development of study protocols.
The involvement of the community should be considered evolutionary. People who have had little experience with scientific research gradually develop an understanding and comfort with contributing to the research process. The first steps may even appear 'tokenistic', but this starting point may be necessary for community interaction to occur.
Important contributions that the community can offer to the protocol development process include identifying obstacles that may arise to informed consent, describing the baseline knowledge of research that exists within the community, and explaining how community cooperation might be facilitated.
Community organizations should play a role in care and support for those enrolled in a trial, in advocacy for the needs of participants, and in developing strategies to prevent discrimination that may arise as a result of participating in a trial.

Controversy:
The group held differing opinions on the stage of research development at which the community should be involved. For some, it is important that this interaction begin as early as possible, preferably before the protocol has been developed. In this way, potential problems would be anticipated and the progress of the trial would be easier in later stages. However, there was debate about what constitutes 'as early as possible'. The point was raised that a sponsor will often have a well-developed methodology prior to the host country being invited to participate. In addition, participants felt that involvement of community members in the stage of protocol development would unnecessarily complicate a process that is already very difficult, and that this involvement should be left for later stages of study implementation. Significant experience is required to write a protocol, community members do not have this experience, the scientific process may be 'distorted' by this step, and a protocol may never result.

3. Ethical and Scientific Review

Consensus:
There must always be both an effective ethical review and scientific review mechanism available in the host country before a vaccine trial may proceed in that country, and these must review all HIV vaccine studies proposed for conduct in that country.

Discussion:
The conduct of vaccine research is not a one-time event but a long-term process of development. The sponsoring country and independent bodies such as UNAIDS should provide support in this area. This support may include formulating guidelines and assistance on how to develop ethical and scientific review capability, developing guidelines on the composition of an ethical review committee, or conducting its own complementary ethical review of a study after it has been evaluated locally.
The community should be involved in the ethical review process.
The distinction of sponsor and host on the basis of nation-states may not be appropriate for this kind of review of research. Sponsors are often multinational corporations, and their country of affiliation may not be clear. In addition, the host may not be adequately defined by nation-state boundaries, but more appropriately as certain populations or communities, hospitals or cities. Use of sponsor and host countries implies developed and developing attributes, and this may be inappropriate. There may be a need to develop a form of international review process.
What ethical review bodies in the country of a sponsor should review proposed research, especially in countries where many bodies at many different levels area available? It was agreed that this process must be independent of the sponsor, but the question of which is the appropriate body was left unresolved. Final approval of a study in a host country, following ethical and scientific review, should follow existing regulations in that country.
It is difficult to determine what representation should exist on ethical review committees, but codifying this representation should occur at the local level with the assistance of international guidelines.

Controversy:
Representatives from the host country could be included on the ethical review body of the sponsoring country, or on the data and safety monitoring board. Some participants shared the opinion that representation on the ethical review committee of the sponsor would be valuable in educating the sponsor on the issues relevant to the host. However, others felt this would not be productive.
In practice, the ethical review mechanism of the host country might be formed immediately prior to the study protocol being reviewed. There was disagreement on whether or not this is adequate for reviewing HIV vaccine trials.
There was considerable controversy concerning the assurance of independence of the ethical review process, both within the host country and the sponsor country. It was generally agreed that ethical review needs to be free of outside influence on the decision-making process (such as from the sponsor company). However, the mechanism for assuring independence, and the bodies that pose the greatest threat to independent decision-making was controversial.

4. Intellectual Property

Consensus:
Although the right to intellectual property (patent and trademarks) has generally rested with the sponsor, the case of HIV vaccines challenges this practice, and there may be a rationale for the host to claim some portion of the right to intellectual property. International collaborators in HIV vaccine research will have copyrights consistent with their contribution. The special case of vaccine trials requires explicit agreements in advance with respect to the sharing of benefits accruing from patents and trademarks.

Discussion:
These issues should be raised in advance of the trial being conducted, and appropriate arrangements negotiated.
In any case, the investigators should have a claim to the data that result from the research, and possibly to authorship and publication.
The body in the host country that has a claim to intellectual property should be made clear. Suggestions included the government, or possibly a non-profit group or foundation.
It may be useful for the host to begin by negotiating rights to a portion of this intellectual property, which would introduce this new concept to the vaccine research process.
A suggestion was made that the host be assisted in developing capacity for data management.

5. Control Arm in Trials

Consensus:
Use of a substance that is not active against HIV in the control arm of a preventive HIV vaccine trial is scientifically and ethically acceptable in the absence of proven effective preventive HIV vaccines.

Controversy:
Some participants were concerned about the lack of benefit that results from being randomized to placebo. It was suggested that another vaccine such as hepatitis B or tetanus vaccine could be given to participants in the control arm, for the sake of increasing benefit. The choice of vaccine would need to be appropriate for the population (i.e. a vaccine should not be given against a disease for which there already exists significant immunity in the population.) However, some participants were of the opinion that those in the control arm should not be treated any differently from those in the treatment arm of the trial. This argument rested on the principle that both arms deserve equal benefit (the treatment arm is not receiving a proven benefit), and that scientific interpretation of the results may be clouded by providing vaccination against a disease other than HIV.
It was suggested that the scientific community might rely too readily on the power of randomized placebo-control trials, and that there needs to be encouragement to consider other study designs that could provide adequate data without the risks inherent in randomization.
In some cultures, participants feel cheated if they are aware they may be receiving a placebo.

6. Informed Consent

Consensus:
Informed consent should ultimately be provided by the individual participant. The issue of informed consent was felt to have been inadequately covered by the study questions and during discussions, given its importance in the ethical conduct of trials.

Discussion:
In the context of discordant couples (the case presented in the scenarios), the group agreed that family and community would need to be involved in the individual's final decision to participate, and many thought that the sexual partner of the vaccinee should also provide informed consent.
Regarding those who suffer from mental disorders, the group agreed that they should not be enrolled in a trial under any circumstances. This does not preclude these individuals receiving a vaccine that has been proven effective following completion of an efficacy trial.
Groups that may have difficulty in giving individual informed consent include bonded sex workers, prisoners, and military recruits.

Controversy:
Differences between the informed consent process in Asia and the West were discussed. There was a strong sentiment among representatives of Asian countries that the degree to which communities must be involved in the decision-making process of the participant and the influence of community leaders on the individual's decision are greater in the East than in the West. There was also concern that study participants in Asia (particularly in rural communities) are more likely to make decisions based on the opinion of the community or its leader than on a thorough understanding of the study protocol. Representatives of Western countries argued that this also occurs in the West, and that the difference between the two cultures is unlikely to be significant. This issue surfaced several times during the workshop.

7. Gender, Pregnancy and Breast-Feeding

Consensus:
Women should be enrolled in preventive HIV vaccine efficacy trials.

Controversy:
Those who are pregnant, likely to become pregnant, or breast-feeding raised special concerns. A majority was of the opinion that this category of women should be excluded from any initial efficacy trial, and enrolled only following phase III trials in other adults and with adequate animal data on teratogenicity. There was concern among a minority that not enrolling women who are pregnant, or excluding those who become pregnant, may delay access for pregnant women to any proven vaccine. It was suggested that it might be necessary to find ways to stimulate parallel research involving pregnant women so that their access to a developed vaccine would not be delayed.

8. Children

Consensus:
Children and adolescents should not be enrolled in preventive HIV vaccine trials.

Discussion:
It was suggested that adult data might be extrapolated to adolescents following completion of a trial. In addition, children and adolescents could be enrolled in later trials after efficacy has been shown in adults.
The age cut-off for eligibility was discussed briefly. It was noted that in some countries the age of legal majority is as low as 12, and that this may not be appropriate for enrolling participants. The definition of 'child' in the International Covenant on the Rights of the Child is under 18 years of age, and this was suggested as an appropriate age for vaccine trials.

9. Protection from Discrimination

Consensus:
There is significant risk of discrimination for participants in HIV vaccine trials in any country. Proactive efforts should be encouraged prior to a trial beginning in order to prevent discrimination.

Discussion:
This discrimination may result from being identified as a participant in the trial, or from vaccine-induced seropositivity. The provision of a card to explain that a person is HIV-positive as a result of a vaccine is not adequate. Proactive strategies for preventing discrimination include changing legislation, advocacy to increase political will and improve enforcement of anti-discrimination laws, education of the public, and utilization of international human rights procedures.
It was noted that in Thailand, even though discrimination on the basis of HIV status is prohibited by law, individuals have been denied insurance after reporting employment with an AIDS organization.

10. Vaccine-Induced HIV-Seropositivity

Consensus:
The sponsor must provide the capacity for differential confirmatory testing for those who develop vaccine-induced seropositivity.

11. Counselling

Consensus:
Risk behaviour counselling, condoms, and syringes, where appropriate, must be provided to participants in a preventive HIV vaccine efficacy trial. The nature of this counselling should be described in the study protocol. Counsellors must be adequately trained to provide the service as described in the protocol.

Discussion:
Counselling must be individual, intensive and comprehensive. Counsellors should be trained and experienced. It was agreed that the counselling 'standard' of the host may not be adequate for the trial situation.
Where there is scientific evidence for the effectiveness of counselling, this should be applied. International standards or guidelines for counselling should also be considered when available.

Controversy:
There was extensive discussion about the degree to which the preventive behaviour counselling should be independent of the investigators. Some felt that counselling should be the responsibility of agencies or bodies completely separate from the investigative authority, whereas others felt that counselling need only be independent of the individual investigators. It was suggested that counselling be contracted to independent agencies.

12. Post-Exposure Prophylaxis (PEP)

Consensus:
Post-exposure prophylaxis should be offered to trial participants to the degree that it has become the standard practice in the host country.

Discussion:
Participants need to be informed about what actions may be taken during the study with respect to post-exposure prophylaxis, regardless of whether or not it is provided without charge.
A major question is who would bear the cost. If the government is funding PEP for the public, then it would be provided through the same mechanism for study participants. If the government is not funding PEP, then they would be left to cover the cost privately.
Those who receive PEP might still be followed in a trial and provide valuable data.
Providing PEP to study participants that is not available to the general population may be an inappropriate inducement to volunteer in the trial.

13. Treatment and Care

Consensus:
For those who contract HIV infection during the course of the trial, but not as a result of the trial, treatment should be provided at a level consistent with that available in the host country. There is no imperative to provide a level of care consistent with that in the sponsoring country, or with the highest available in the world.

Discussion:
It may also be inadequate to provide exactly the same care as that in the host country. As an example, it was considered inappropriate not to use sterile needles for administering the trial vaccines, although sterile equipment may not be generally available in the host country.
It was agreed also that there is some obligation for the sponsor to provide treatment in proportion to its resources. Where treatment is provided to participants, it should be provided to all participants. In the case of discordant couples, it should be provided to the HIV-positive partner.
There was significant concern about the risk of disproportionate treatment resulting in undue incentive/inducement for people to participate.

There was concern that a sponsor providing excessively high levels of treatment could exonerate a government from its responsibility to provide treatment for its population.
It was acknowledged that providing treatment at a level consistent with standard practice in the host would make the conduct of trials in developing countries financially attractive to potential sponsors. However, this was viewed by some participants as an acceptable way to attract research activity to a developing country.

14. Compensation

Consensus:
Social harm through stigma and discrimination is more likely to occur than physical harm in an HIV vaccine trial. This must be identified in the study protocol, along with information on how the sponsor intends to deal with this kind of damage.

15. Availability of Vaccine

Consensus:
The sponsor has an obligation to the host regarding availability and pricing of the vaccine. Availability should be negotiated prior to the protocol being approved, with a statement of assurance of availability included in the contract, even if details are not yet possible.

Discussion:
Negotiating availability might include consideration of claim to the patent.
First priority for providing vaccine following the trial goes to those who received the placebo.
Mechanisms were discussed such as transfer of technology to the host to ensure the ability to produce the vaccine, tiered pricing, an international loan fund, or partial responsibility for production by the host (product refinement or packaging).
UNAIDS should promote international activity around resource allocation, and should begin this soon.
There should be an agreement that if, for any reason, the sponsor decides not to produce the vaccine following trial completion, another country could produce it for its own use.

Entebbe, Uganda, 27-29 April, 1998

1. Phase I/II (Safety and Immunogenicity) Trials

Consensus:
A given study should reflect the needs of the host country, and the decision to undertake the study should rest with the host country. In most cases, phase I/II trials should be conducted in a sponsor country prior to being conducted in a host country, especially if the infrastructure in the host country limits its ability to determine the safety and immunogenicity of a candidate vaccine. However, in a significant minority of cases, conditions in the host country may warrant the conduct of a first phase I/II trial, to be carried out with the requisite scientific rigor. In addition, phase I/II trials should generally, but not necessarily, be repeated in a host country prior to phase III trials in that country in order to examine safety and immunogenicity in the local context of human genetics, nutrition, coexisting diseases and prevalent viral subtypes. Repeating phase I/II trials will also have the benefit of building experience, knowledge, understanding and infrastructure among the public, the government and the scientific community prior to a phase III trial.

Discussion:
Scientific data for the candidate vaccine need to be examined by a scientific review body in the host country. It was acknowledged that there is not currently consensus within the scientific community about what level and type of immune response is likely to identify an effective vaccine.
Community representatives need to be involved in the evaluation of a candidate vaccine being considered for a trial in the host country. This might be accomplished through community representation on the scientific review committee.
A list of conditions under which a trial may be conducted in a host country should be developed, and must include adequate ability to conduct scientific and ethical review. International bodies such as UNAIDS should play a role in developing these guidelines and assisting countries to develop capacity.

Controversy:
Should a country like Uganda, which now has considerable infrastructure developed, be prohibited from conducting a phase I/II trial prior to the same trial being carried out in a sponsor country? The purpose would be primarily to ensure that problems with safety are dealt with before subjecting individuals in the host country to potential harm. Does a country like Uganda require this protection? Or, is there a point where the host country should be able to determine on its own whether it will accept the risks of conducting the first phase I/II trial? This was identified as an important issue for Uganda. Some felt that a country such as Uganda should consider taking the step of conducting a phase I/II trial even if the same trial has not previously been conducted in a sponsor country. One circumstance in which this might be appropriate is where the candidate vaccine targets a viral subtype not present in the sponsor country. In addition, this could speed up the process of vaccine development, as the phase I/II trial would only need to be conducted once, rather than being repeated in the host following trials in the sponsor country. It was pointed out that it might be important to make a distinction between a trial for a new vaccine 'concept' and a trial for a new 'product' for which the concept has already been tested (e.g. a change in subtype specificity for a gp120 candidate that has already had phase I/II trials in a sponsor country for a different subtype).

2. Phase III Trials

Consensus:
It is reasonable to conduct a phase III efficacy trial in a developing host country even if the candidate vaccine is not likely to be in a phase III trial in a sponsor country, under certain conditions (see discussion below).

Discussion:
In determining the appropriateness of a candidate vaccine for a phase III efficacy trial, a host country must consider the safety and immunogenicity of the candidate vaccine, the applicability to the prevalent viral subtypes, feasibility of conducting the trial, and the context of the population in terms of HIV epidemiology, economic resources, and availability of HIV treatment options. Considering all of these, it is conceivable that a vaccine that does not seem appropriate for testing in a developed country could be accepted for a phase III trial in a developing country. However, this is only possible under the condition that there is capacity to conduct scientific and ethical review in the host country, and that application of ethical principles is in some way assured.
No phase III trial should be conducted on the basis of desperation and urgency alone.
Development of a phase III protocol should be an evolutionary process, involving stakeholders, the community likely to be participants, the community surrounding these potential participants, lawyers, and government as early as possible.

3. Vulnerability to Harm and Exploitation

Consensus:
There are certain attributes that may render a community vulnerable to harm or exploitation from conducting preventive HIV vaccine trials. These attributes include, but are not limited to, the following:

- large disparity between classes
- advanced poverty
- lack of understanding of or experience with scientific research
- restriction in communication, or inability to access or understand appropriate information
- inadequate human rights protection (lack of legal framework and safeguards) to prevent discrimination based on HIV status
- market forces such as competition between companies
- a situation of temporary restriction of rights (such as prison)
- inadequate infrastructure such as transportation
- situation of war or extreme political instability
- dictatorship, which forces decisions based on political factors
- inability of an individual to act or decide independently (such as where an 'opinion leader' strongly influences a group, or cultural inability of a woman to make a decision independently of husband or father)

Discussion:
Those individuals, communities or countries characterized by any of the attributes listed above should not be excluded from HIV vaccine research, but may require additional safeguards to ensure that harm or exploitation does not result from the research.

4. Community

Consensus:
It is important that the community be involved in the process of protocol development, in decisions to start trials and in scientific and ethical review. Community members (including government, potential participants, the general public) should receive adequate information and education beginning early on.

Discussion:
It is important to include those participating in HIV vaccine trials, those who will potentially participate in trials, and community leaders (or 'opinion leaders', people whom the potential participants listen to).
Where there is disagreement among community representatives, a majority opinion should be accepted. In addition, it is important to pursue consensus through further consultation.

5. Ethical Review

Consensus:
A host country that is considering conducting any phase of an HIV vaccine trial must have the capability to conduct its own ethical and scientific review of the proposed protocol. This review must be independent of parties that may have potential to gain from the outcome of the trial (such as investigators, those who may benefit financially, and those who may benefit politically).

Discussion:
Although governments will justifiably have an interest in the outcome of HIV vaccine research (unlike some other forms of scientific research), there is a need to ensure that the ethical and scientific review process can be conducted without influence from government. This may be accomplished through formation of independent government commissions or through legislation that defines the role and independence of the review bodies. Potential for political interference must be minimized. Various current government arrangements were described for the African region. In some, the head of government must sign the protocol before it proceeds, and the correctness of this practice was challenged by the group.
Ethical review should include representation from the community, as described above. Guidelines on the composition of ethical review committees for HIV vaccine trials should be developed and followed.
International organizations have an important role to play in the development of ethical review guidelines and in assisting countries to build ethical review capacity.
There is currently no mechanism for quality assurance of the ethical review process, or for enforcing adherence to guidelines. Should this be developed?
Where ethical and scientific review capacity does not exist, it should be established prior to conducting HIV vaccine trials. The role of international bodies in the review process requires examination. Where applicable, international review bodies may review protocols that are to be conducted in 'developing' countries. As a matter of principle, the final decision on whether to participate in a trial must rest with the host country, provided that the requisite capacity is in place, as outlined above.

6. Intellectual Property

Consensus:
In general, an HIV vaccine manufacturer will have claim to intellectual property (patent and trademark). However, there may be situations in which the contribution of the host country to the vaccine development process is significant enough to justify the country having claim to intellectual property. An arrangement should be negotiated prior to conducting the trial.

Discussion:
A host country might consider negotiating technology transfer, recognition of stakeholders in publications, a claim to 'spin-off' developments (such as new assays or other scientific advances) or a share of the proceeds resulting from sale of the vaccine.

7. Control Arm in Trials

Consensus:
Any preventive HIV vaccine trial must include risk behaviour counselling and provision of condoms for all participants, as this is currently the only known effective prevention intervention. It is scientifically preferable, and ethically acceptable, to use an inactive substance as a control for the vaccine, as long as there is no other effective HIV vaccine available.

Discussion:
A question was raised concerning what should be included in the control arm if a vaccine proven to be marginally effective against HIV was available. There was limited discussion on this, but some were of the opinion that the proven vaccine should be used regardless of level of effectiveness.

Controversy:
The group was divided on whether it was ethically acceptable to provide no benefit beyond counselling to those in a control arm, and some felt that it would be preferable to administer a vaccine with proven effectiveness against another disease, such as hepatitis B. It was pointed out that this may need to be viewed as an additional vaccine trial for hepatitis B (with the control arm for the hepatitis B trial being the candidate HIV vaccine arm), and that appropriate analysis would need to be carried out. The opposing point of view was that it would not be ethical to provide a beneficial vaccine to those in a control arm while there is no proven beneficial substance being given to those in the treatment arm.

A suggestion was to consider having three arms in the trial, one using candidate HIV vaccine, one with inactive substance, and one with a public health vaccine such as hepatitis B.

8. Informed Consent

Consensus:
Individual informed consent is necessary for those participating in preventive HIV vaccine trials. There are situations that make this difficult, and these require that special efforts be made, but in no case should anything be substituted for consent of the individual.

Discussion:
Situations that may make individual informed consent difficult include those in which an individual requires the approval of another person or group in order to make decisions, where there is coercion, and where there is a cultural tradition of sharing of risks and responsibilities. (Examples raised were marital relationships, parental control of women, and community, religious, and political influences.) Where these situations arise, effort may be required to educate a community and develop understanding prior to requesting informed consent of individuals. Where women are not permitted to act independently, they are still capable of providing valid informed consent.

In cases where it remains unlikely that adequate individual informed consent will be achieved (such as in the situations listed above, or in cases involving mental disability), exclusion from participating in HIV vaccine trials should result.

There was extensive discussion of the specific situation of discordant couples, as outlined in the case scenario. Should the HIV positive partner also be enrolled in the trial? The group generally felt that the partner should at least be included in the counselling, and that it may be preferable that the partner also provides informed consent. The potential for the HIV-positive partner to either coerce or discourage the HIV-negative partner to participate was raised. There may even be risk of harm to the volunteer incurred by the partner if the participant does not follow the wishes of the partner. The group agreed that in no case should unwilling individuals be enrolled in a trial in which they do not wish to participate. In addition, if they do wish to participate, but risk disapproval of the partner (and have accepted this risk in providing informed consent), then there is no ethical imperative to protect them from this disapproval in any way other than by providing adequate counselling and support.

9. Counselling

Consensus:
High-quality risk reduction counselling must be offered to all participants in an HIV vaccine efficacy trial, and should be provided independently of the investigator. Counselling capability should be part of the initial capacity-building process prior to a trial being conducted.

Discussion:
Independent monitoring of the quality of the counselling should be considered.
There should be standardization of counselling in some way. It must also be specific to cultural diversity and social norms. A country such as Uganda has extensive experience with this, but many others do not. They may need such international guidelines as standard formats, questionnaires, and training.

10. Gender, Pregnancy and Breast-Feeding

Consensus:
It is ethically required to include both genders in preventive HIV vaccine trials, unless a scientific rationale warrants otherwise. If there is any consideration of enrolling pregnant or breast-feeding women in trials, then there must be adequate methodology to ensure that valuable data may be gained from their inclusion.

Controversy:
There was disagreement on whether women who are pregnant or breast-feeding should be enrolled in HIV vaccine trials. One argument was that including them provides important data on safety and efficacy that will not be gained otherwise. In addition, women are capable of understanding the risks to themselves and their fœtuses and should be able to make the choice of whether or not to participate, through providing informed consent. The opposing view is that the fœtuses and neonates should be protected from any potential harm as a result of participation in the trial, and that investigators have an obligation to exclude these women until adequate safety data is accumulated. Some argued that these data would not be accumulated, or would certainly be delayed, if these women were not included in the initial trials.
The role of the father in determining the involvement of a pregnant woman was identified as important, but not discussed in depth.

11. Children

Discussion:
The group recognized the importance of children and adolescents in HIV vaccine trials, but was unable to adequately discuss the issue due to time constraints. One group proposed that children of mothers who received the candidate vaccine should be enrolled in the trial for collection of data only, but that children should not generally be enrolled in a trial until following successful completion of a phase III trial in adults. This is because they cannot give adequate informed consent. However, the ages at which childhood effectively begins and ends was not defined.

12. Discrimination

Consensus:
Discrimination may result from a vaccine-induced positive test, and steps must be taken to reduce or eliminate this. Discrimination might be the same as for those who are infected with HIV. Preventive steps should be taken, through advocacy, creating protective legislation and ensuring its enforcement. Measures such as providing a card to the participant that explains a vaccine-induced positive status may also be helpful. The sponsor has an obligation to provide differential HIV antibody testing infrastructure in the host country.

13. Treatment and Care

Consensus:
Treatment and care must be provided to study participants who become infected with HIV during the course of the trial. The appropriate type and level of treatment should be decided upon by the host country. It is not necessary that the type and level of treatment coincide with that which is generally available to the population of the host country, nor that available to the population of the sponsor country, nor the highest attainable worldwide. However, it must be made reasonably available for the lifetime of the participants.

Discussion:
It might include immunologic monitoring, physician visits, prevention and treatment of opportunistic infections, and palliative care, but not necessarily antiretroviral therapy.
One suggestion for determining the appropriate level of care for participants was to use as a benchmark the highest level of care available in the host country, which would probably be that available through private mechanisms. However, this could still result in a standard that is not achievable or sustainable due to cost. Although there was general agreement that the standard that was chosen would need to be sustainable, the group did not develop other specific approaches to determining level of care for participants.

14. Endpoints in Vaccine Trials

Consensus:
It may be difficult to measure secondary endpoints in populations where early antiretroviral therapy becomes common practice. However, it is not ethical to conduct a trial in a given population solely for the purpose of avoiding populations where early treatment is used. There may be situations in which there is additional scientific justification for conducting the trial in a population without early treatment. It may be reasonable to conduct a phase III trial simultaneously in a country which provides early treatment, as well as one that does not, in order to gather secondary endpoint data from both and compare outcomes.

15. Compensation for Injury or Harm

Consensus:
The circumstances under which compensation will be provided, and the type and level of compensation, must be described in the study protocol and in the information for consent.

Discussion:
Discussion centred primarily on harm of a social nature. Socially adverse events will generally result from discrimination based on perceived or actual HIV status. There needs to be adequate individual counselling and sensitization of the community to issues that may arise through involvement in HIV vaccine trials.
Where social harm results from apparent breach of confidentiality, it would be important to determine whether there was negligence on the part of the research team. Although this may be very difficult to accomplish, attempts should be made to do so, and compensation should be provided for cases where negligence was involved.
It was suggested that a Data and Safety Monitoring Board might take the responsibility of determining whether negligence was involved in a specific case or not, though it was acknowledged that this would be a new practice for such a body.
It was suggested that there needs to be a mechanism to ensure exclusion of those individuals who do not have an adequate understanding of the potential risks of participation in the trial.

16. Access and Availability of Vaccine

Consensus:
Those who have participated in an HIV vaccine trial, and the population of a host country in which the trial was conducted, must have access to the vaccine being studied if it is proven efficacious. Access for other groups (such as high-incidence populations in other countries, other developing countries) should be negotiated prior to the trial being conducted.

Discussion:
Those who should be involved in negotiating availability include government (health, finance, and justice), investigators, sponsors, the pharmaceutical industry and international organizations such as UNAIDS.
The level of assurance of availability that can be made prior to the results of a trial becoming available, and how this assurance can be guaranteed, is difficult to define. Without knowing the level of effectiveness, cost of production and appropriate target populations, detailed formulae for ensuring availability may not be achievable. This issue was not discussed in detail.
If a more effective vaccine is discovered than that being studied in the host country, the host country must have the option to use the more effective vaccine.

ANNEX 1: Case Scenario and Discussion Questions

Case Scenario

1.

A pharmaceutical company, (the 'sponsor'), is based in a developed, industrialized country (the 'sponsoring country'). The sponsor is proposing to conduct a phase III vaccine efficacy trial of an experimental preventive HIV vaccine (the 'candidate vaccine'). The sponsor has conducted pre-clinical trials in animals, and it has completed a phase I clinical trial for safety in human subjects in the sponsoring country. It has also completed a phase II trial for safety and immunogenicity in the sponsoring country. The results of these trials suggest that the candidate vaccine is safe, immunogenic, and potentially effective. They show that markers for humoral immunity are induced by the candidate vaccine, although cell-mediated immune responses are not consistently present. A safety board of the sponsor has determined that the candidate vaccine is safe for further trials. The company's position is that the only way to know if the vaccine is effective in preventing HIV infection is to study it in a phase III human-efficacy trial.

The sponsor claims that it will require a very specific population from which to recruit volunteers. The most important characteristic of this population is that it must have a relatively high number of new infections occurring over time (a high incidence). Otherwise, it would require a very long time and a very large sample size for any difference between the placebo-treated and candidate vaccine-treated groups to be observed. This population should be composed of individuals who have adequate social stability, so that they will be more likely to continue participating in the study until its completion, and will be capable of following the study protocol. They must be capable of providing informed consent. In addition, the sponsor points out that any HIV vaccine will ultimately have its greatest value in these same high-incidence countries, and that the need for a vaccine in these countries is urgent. It is important that the vaccine be effective against viral strains found in developing countries, and in the human genetic, nutritional, and environmental context of these countries. For all of these reasons, the sponsor proposes to conduct the trial in a developing country.

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2.

There is a potential host country with which the sponsor has been in discussion. The host country has been working for several years to identify an appropriate study population (a cohort) in anticipation of a possible vaccine trial. This was required to ensure that there is a reasonable estimate of the incidence of new infections in the population, that the population is one that can be followed at regular intervals, that predominant viral genetic strains are identified, and that baseline HIV risk behaviour in the cohort is described. There appears to be a cohort which is appropriate. However, there has been no phase I or phase II study of this candidate vaccine, or any others for that matter, conducted in the proposed host country. Investigators in the host country are convinced that the need for a rapid process of vaccine evaluation is great, and that delaying the process in order to conduct phase I and II trials in the host country will mean the loss of too many lives. They are advocating for a phase III trial to take place in the host country without phase I and II trials in that country.

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3.

The research protocol that the sponsor is proposing has resulted from several levels of collaboration. Clinical research physicians from the company have carried out discussions with investigators from a university in the host country. These are the same investigators who have been attempting to identify an appropriate cohort for the trial. Investigators from this university have been enthusiastic about the proposed trial, and do not feel that there are major obstacles. They have participated in the development of the protocol and of the informed consent procedure. Community consultation was carried out by host country investigators during the cohort development study, and HIV-infected individuals and people in high-risk groups were asked for their opinions on logistics and ethics related to carrying out the cohort study. Much of this consultation was facilitated by nongovernmental organizations (NGOs) involved in HIV education and prevention. Based on these consultations, the host country investigators have advised the sponsor on how the protocol should be designed. However, there has not been any consultation of the community specifically related to preventive HIV vaccine trials, or on this specific protocol.

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4.

The sponsor has completed the process of scientific review of the proposed trial protocol through a university-based scientific review board in the sponsoring country. However, there is not a comparable review board in the proposed host country. The sponsor is now pursuing ethical approval from an ethical review board, also in the sponsoring country. There is no capacity for formal ethical review in the host country. The investigators there do not perceive that this should be an obstacle to proceeding with the trial, provided that the protocol has been developed with consideration of the input given by the host country investigators. The host country investigators are satisfied with the scientific and ethical aspects of the protocol.

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5.

The sponsor has agreed to train local technicians and interviewers and to provide the host country with the necessary clinical and laboratory infrastructures for research requirements, including logistical support. There will be no expense to the host country for conducting the trial. Investigators there have put considerable effort and expertise into developing the potential trial cohort, and the actual details of the current trial protocol. Without their support, in fact, it is likely that the current trial proposal would not have been possible. They are concerned that, at the completion of the trial, they may have no right to the results of the trial as intellectual property.

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6.

The sponsor proposes a phase III efficacy trial in which the vaccine candidate will be given to some individuals, and a placebo will be given to others. Neither the participants, the investigators nor the sponsor will know who is receiving the HIV candidate vaccine and who receives the placebo until completion of the trial (a randomized, double blind design). The sponsor states that this is the only way to arrive at valid and powerful conclusions about the effectiveness of the vaccine. It claims that no other study design will be capable of contributing conclusive evidence.

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7.

The cohort that has been proposed is a population of “discordant” couples. These are heterosexual couples in which one of the individuals is infected with the HIV virus, and the other is not. It has been discovered that there is a relatively high incidence of new infections occurring in the previously uninfected partners, in spite of counselling on how to avoid transmission. In addition, this population appears to be capable of following a research routine and presenting for research visits.

The sponsor and investigators in the host country propose that couples such as these be invited to participate in the trial. There will be advertisements distributed to key sites inviting people to participate in the study. Those who contact the investigators will then receive both verbal and written information in their own language about what the study is, how it will be carried out, and what the potential risks and benefits to the participants are. Both members of the couple will receive this information, but only the HIV-negative member (male or female) will be invited as a study participant. They will be asked to provide their signature to consent to participate in the study if they have completely understood the trial procedures and agree with them. They will have the option of leaving the study at any time. The investigators have assured the participants that all information will be kept in confidential files with the investigators and not with the country's health care system.

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8.

The following details will be described to the potential participants prior to consenting to the study. After they have signed the informed consent for testing (to determine if they are eligible for the study), both members of the couple will require an initial HIV test. This will confirm that one is positive and one negative. They will also need to answer several questions about their sexual activity within the relationship and outside of it. If both are found to be positive, then neither one will be eligible to enter the study, and both will be counselled on how to seek HIV care that is available in the host country. However, if one of the partners is confirmed to be HIV-negative, then this individual will be invited to participate in the trial. The HIV-positive partner may participate in the study visits, and will be encouraged to participate in preventive counselling, but will receive no further testing or questioning. After the HIV-negative partner has consented to participate in the study, he or she will answer a further questionnaire requesting more detail about sexual history, drug use, social activities, and many other personal details. The participant will then receive an injection in the arm. Neither the participant nor the investigators will know whether this injection contains the vaccine being tested, or the placebo. There may be some pain in the arm for the next couple of days, and possibly fever, but it will be mild and will subside. There are no other side-effects to be expected, but if any symptoms should arise that have not been described, the participant is asked to notify the investigators. There is <u>no risk</u> that the injection will <u>cause</u> infection with HIV, as the candidate vaccine is basically composed of inactive pieces of the virus. However, there is a possibility that any future tests for HIV will indicate a positive result even if the individual is not truly infected. If this occurs, the individual may have a positive test for some weeks even though they are not truly infected. For those who do have a vaccine-induced seropositivity test, they will need to take a special blood test (Western blot) to prove that they are not truly infected. This test is usually, but not always, available in laboratories doing screening. Participants who wish to have it will carry a card explaining to health workers that their HIV screening test is not evidence of infection. Finally, if this candidate vaccine is found NOT to be efficacious, then there is a remote possibility that another candidate vaccine that is found in the future to be effective may not be useful for an individual who has already received the current study vaccine.

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9.

The HIV-positive partner will receive no injection, and is not officially enrolled in the study, but both members of the couple will be offered counselling on how to avoid transmission. It is emphasized that there is a chance that the participant has not received the candidate vaccine, but that even if he or she has received the vaccine, it should not be assumed that it will provide any protection. The couple should use every possible method, including condoms, to prevent transmission of HIV, and condoms will be provided by the sponsor at no cost to the couple. Study visits will take place at 7 days, 14 days, and 30 days after injection, then every 3 months for the first year and every 6 months for another 4 years. These visits will include a short interview (which includes questions on sexual activity, number of partners, use of barrier techniques), a blood test and

counselling on how to prevent transmission of HIV. The blood test will be for the presence of new HIV infection, as well as immunological markers (such as CD4 cell count and viral load). If the participant does become infected, they will be asked to continue with the research visits for at least 12 months following infection. Over these 12 months, they will continue to have blood tests every 3 months to see how much virus is in their bodies. During this time, they will also be encouraged to seek the treatment, which is available through the health system of their country.

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10.

The proposal does not include any provision for antiretroviral drugs, prophylaxis or treatment for opportunistic infections, physician visits, palliative care or monitoring of the immune system for the HIV-positive partners, or for the study participants should they become infected with HIV during or after the study. The sponsor does not take responsibility for any special testing required by those who develop a positive HIV test as a result of receiving the candidate vaccine. The HIV positive partners will be encouraged to pursue the standard clinical treatment that is offered in the host country, as will the HIV-negative partners should they become infected during the course of the trial. All costs for transportation to the research visits and any expenses related to the visit such as food and lodging will be covered by the investigators.

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11.

If there is any physical illness or injury to the participants that results directly from the research being conducted, the costs for treating this will be covered by the sponsor. However, the proposal does not include any provision for compensation for loss of employment or other social disruption related to involvement in the research, or for stigma or discrimination resulting from an altered HIV testing status, or acquiring HIV infection.

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12.

If, following the three years of the trial, this vaccine is found to be effective, the sponsor has agreed to enter into a discussion phase with the government and health authorities of the host country concerning provision of the vaccine to that country. It is recognized that a decision about how and for whom the vaccine should be provided will depend to large degree on results to be obtained from the study, such as side-effects and degree of effectiveness. A promise about providing the vaccine cannot be made until this information is available. However, the sponsor is willing to ensure that the vaccine is made “reasonably available” at affordable rates to the individuals in that country for whom the vaccine is most appropriate.

Discussion Questions

1a. Collaboration Considering only the scientific aspects of this vaccine, what would constitute an appropriate candidate vaccine for an efficacy trial in a country ("host country") other than where it was developed ("sponsor country")? The sponsor is clearly convinced that this one is. Who else should review items such as the safety data and immunogenicity data? Who should decide which candidate vaccine is appropriate for study in human subjects in the host country? Is this primarily an issue that the scientific community of the sponsoring country or agency should deal with, or are there other sectors that should be involved in the decision? Is this a step that requires the consultation of government leaders, the population at risk for infection, or the scientific community of the host country?

1b. Collaboration Apparently there is another candidate vaccine being developed by another company that has not been collaborating with this host country so far. From animal studies, there is a possibility that this vaccine will be more effective, but another year is required before the phase I and II trials are complete. Now there is a question of whether the host country should wait for the next vaccine, and whether it should try to collaborate with the other company. Who should be involved in this decision? What criteria must be considered to determine which candidate vaccine enters a Phase III trial in the host country first?

1c. Collaboration One of the purposes of current international ethical guidelines for conducting scientific research in human subjects is to ensure that vulnerable communities are not exploited or treated unfairly through the conduct of the research. "Developing countries" have been considered vulnerable communities, but the definition of a developing country is often difficult to agree upon. It may be more helpful to identify the characteristics of a country or community that make it especially vulnerable to harm or exploitation from scientific research that does not originate from within that community. What are these characteristics? (Consider issues of economics, political systems, human rights protection, power of individuals, infrastructure for scientific research and for scientific and ethical review, and others.)

1d. Collaboration The sponsor has stated that it is important to have a high incidence population for this trial, and that the candidate vaccine should be tested in a population where the developing country viral strains are common. This will make the trial shorter, meaning an answer will be available sooner, and it will, of course, be less expensive. Some would say that research in developing communities should not be carried out if it could be conducted reasonably well in developed communities. Is the rationale for conducting this trial in a developing country adequate?

1e. Collaboration It may be argued that there is a greater urgency to identify a vaccine for developing countries than for developed countries, due to a higher burden of disease and lack of affordable treatment. Does this urgency make it ethical to test a candidate vaccine in developing countries that would not be considered in a developed country because of insufficient evidence that it will be effective? Why or why not?

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2a. Collaboration Some experts would argue that there are advantages, such as development of expertise and infrastructure, which make carrying out Phase I and II studies in the developing country a benefit in spite of the delay in initiating a phase III trial. Should the sponsor be obliged to conduct phase I or II studies in the proposed host country before moving ahead to phase III? If so, should Phase I and II studies in the host country be conducted simultaneously, or following, the same trials in the sponsoring country?

2b. Collaboration The sponsor has not proposed that a phase III trial be conducted at the same time in a developed country. Is this reasonable? Why or why not?

****

3a. Collaboration Is it important to consult the "community" on aspects of an HIV vaccine protocol as it is developed even in early phases of development? Who are the important community players to include ("at risk" individuals, key informants, grass roots organizations, host-country investigators, government?) What if various spokespersons for the community disagree? How should such disagreement be resolved? What are the advantages and disadvantages of conducting this consultation? At what points in the process of protocol development is it most important to have community input?

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4a. Collaboration Should any form of ethical review capability be available in a host country before HIV vaccine research can be carried out there? Who should be deciding whether it is ethically appropriate to conduct a study in the host country? What process should be initiated in order to ensure adequate scientific and ethical review from sponsor, host and international bodies?

4b. Collaboration The ethical review committee of the sponsoring country has no representatives from any developing communities. However, the proposal is eventually approved and the government of the host country also approves the trial. Is this process sufficient to ensure that the relevant ethical issues have been adequately explored and dealt with? If not, what additional steps might be needed?

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5a. Justice Who should have the rights to intellectual property related to collaborative HIV vaccine research?

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6a. Collaboration Is it reasonable to use placebo in the control arm of a preventive HIV vaccine trial? What would constitute the most ethically acceptable control arm for this trial (inert substance, hepatitis B vaccine, other vaccines?)

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7a. Protection Individual informed consent has been promoted as an important step in ensuring that study participants voluntarily agree to be subjects in research that may not benefit them and might even cause harm. Are there cultures where it is difficult or impossible for an individual to act independently, and where consent of the community or a recognized community leader might also be required? Is there a valid concern that women in some cultures, where the right to exercise self-determination is in question, may not be able to give valid informed consent for research? What should be the approach to obtaining informed consent from women in those cultures where women are normally not permitted to make independent decisions on their own behalf?

7b. Protection The ethics committee has raised the point that there may be some individuals who are incompetent to give consent due to mental handicap or mental illness. Is third-party permission a reasonable alternative in these cases? Would excluding such individuals be unjust because they would be denied a "right" to participate in an HIV vaccine efficacy trial?

7c. Protection The consent form makes it clear to the potential participants that this study has been sponsored by another country (which is named), and that scientists from this country have developed the vaccine and the protocol. Is there a risk of this being an undue incentive to participate?

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8a. Protection It is said that this vaccine is not likely to cause any harm to fœtuses or breast-feeding children, but the data available on this are still very limited. Should women who are pregnant, nursing, or of childbearing potential be enrolled in preventive HIV vaccine trials? Do any of these groups require special protection?

8b. Protection Is there any situation in which the potential benefit would justify enrolling children in an HIV vaccine trial?

8c. Protection What kind of discrimination might arise from a person developing a vaccine-induced positive HIV test that could be detected on later screening? What sorts of legal protections, if any, should be in place before a vaccine trial is permitted to proceed?

8d. Protection It may be difficult in some countries for study participants who develop a vaccine-induced positive HIV test to obtain the more specific confirmatory test (Western blot). Does the sponsor have any obligation to provide this test to these individuals? Why or why not?

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9a. Protection A researcher might be regarded as being in a fiduciary relationship with a study participant, that is, a relationship of trust and confidence. If this is the understanding, then neglecting to provide counselling on prevention of HIV transmission or possibly barrier methods to study participants might be considered a breach of trust, and an unethical approach. However, this illuminates a conflict of interest between participant and researcher, as the very success of the research depends on there being a relatively high risk of new infections. How might this conflict best be addressed to ensure the protection of the individual in spite of the goals of research?

9b. Protection How should risk counselling for preventing HIV transmission be carried out in a study situation such as this? What would constitute an adequate 'standard of counselling'? Should the method and scope of counselling be compatible with what is routinely available in the host country? In the sponsoring country? Is there another standard that should be followed?

9c. Protection One year into the study new evidence is available, and it becomes the standard of care in developed countries to provide post-exposure prophylaxis with antiretrovirals following unprotected sexual encounters with known HIV-positive individuals. The host country is debating whether to make this a policy in its population. Should this new approach now be integrated into the study and provided by the investigators, or should a decision be left to see what becomes the adopted public health policy of the host country?

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10a. Collaboration One member of the ethical review committee is convinced that the participants who become HIV-positive should receive all of the HIV treatment that would normally be available in the sponsor country. Because the study is being initiated by a developed country, the developed country's "standard of care" should be implemented. Another member of the committee points out that this will be extremely expensive, and that no one else in the host country receives this level of treatment. Should participants who become infected receive any therapy other than what others in the host country would normally receive? Why or why not?

10b. Collaboration If the answer to the above question is YES, then what "standard of care" should be considered the most appropriate? There are many examples of therapeutic regimens that have been adopted as "standard of care" in one developed country but not in another (e.g. antibiotics for ear infections and early antiretrovirals for HIV). It often takes many years of a treatment being

used by many people before enough information is available to consider the treatment the "best available". In fact, the value of many treatments, which have been available for a long time, is still not agreed upon among experts. At what point does any therapy gain the status of being the "best proven?" Are there criteria, or is there a level of international consensus, which might be used to determine which therapies should be considered universally standard from a scientific point of view?

10c. Collaboration If therapies other than those normally available in the host country should be offered, which ones are most appropriate in this situation? Should there be immunological monitoring, regular physician visits, prophylaxis or treatment for opportunistic infections, palliative "comfort" care? What about antiretroviral treatments? Should combination antiretrovirals be available, and should they be given early in infection as they are in some countries, or further into the progression of disease as they are in other countries? Should post-exposure prophylaxis be considered for unprotected sexual encounters with known HIV-positive individuals, as is being debated in some countries now? If there is an obligation to provide this, then how long does this obligation last? Until the end of the study or potentially for an unlimited period? Does the obligation extend to the initially HIV-positive partner in the case of this study proposal or would only the participant receive therapy?

10d. Protection Another member of the ethical review committee argues that, if a high level of medical care is assured to the HIV-positive partners, or to those who become positive in the study, then people will be eager to join in the study, even if they are not convinced that the study itself is a wise decision for them. What level of reimbursement is reasonable in a developing country and what might be considered an unacceptable inducement? What factors are important to consider in deciding the level of reimbursement that is reasonable?

****

11a. Justice One of the participants became infected with HIV during the study. It is not possible that this was a result of the candidate vaccine, and it is not known whether the participant received candidate vaccine or placebo. However, this man claims that he understood the injection was to protect him from HIV, and that he began having unsafe sexual activity following the injection. Is there any rationale for this man receiving compensation?

11b. Justice One of the participants developed a positive HIV test following the injection. Although it was very clear that this person did not truly have HIV, and this was marked on the person's research record, she became anxious about the change and finally could not work at her job any longer due to the stress of the situation. Should the sponsor provide compensation for this incident? What if the person was not stressed by the incident, but the information about having a positive HIV test leaked out and the community of the participant began to turn away from her and discriminate against her? Is this a form of damage that should be compensated?

11d. Justice In any of these situations, if compensation seems reasonable, what is the obligation of the sponsor to the participant's family, if the participant has been the family's primary source of income?

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12a. Justice Is it reasonable to give any assurance to the host country concerning availability of the vaccine following completion of the research? Who should receive assurance of availability (e.g. trial participants who received placebo, family members of participants, all high-risk members of the host country, other developing countries)? What are the criteria for determining that a vaccine is "reasonably available"?

12b. Justice At the trial's completion, it is discovered that this candidate vaccine is about 50% effective in preventing HIV. In other words, a person receiving the vaccine will have their risk of acquiring infection reduced by half. During this trial, another candidate vaccine started in a phase III trial in a similar country, and preliminary data suggest it may be more effective. Should the sponsor of the trial follow through in supplying the first vaccine to the host country? Should the host country be obliged to use this vaccine?

12c. Collaboration In what ways could the sponsor, the host country, and international organizations work together to ensure the best formula for supplying the final product to the host country, recognizing that much of this discussion will happen before important data are available?

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General Issues :

13a. There are many reasons that a vaccine manufacturer may wish to conduct a preventive HIV vaccine trial in a developing country. It is most likely less expensive to do this; it may be easier to get official permission from a developing country; and it may diminish the manufacturer's product liability exposure. In addition, as discussed, there is likely to be a higher incidence, specificity of viral strains, different human genetic patterns, environmental and nutritional factors and public health urgency. However, one other reason that this trial may be difficult to conduct in a developed country is the need to measure "secondary endpoints". This refers to the ongoing measurement of viral load and immune function in participants who become infected with HIV while in the trial. It is expected that no vaccine will be 100% effective, but it is possible that even without preventing infection, it could still be very effective in keeping viral levels low in individuals who do become infected. In some developed countries, antiretroviral treatment is recommended at the first diagnosis of infection. This policy could interfere with measuring secondary endpoints, and thus with discovering a very useful attribute of a vaccine that might not prevent infection.

If there was agreement (which there is not) that early antiretroviral therapy was the best treatment, this would clearly raise a conflict of interest between investigator and participant, as the goal of the research would be better served by NOT providing the best treatment. It is unlikely that most developing countries will be able to afford these expensive treatments, and it may be suggested that conducting the trial in a developing country unethically takes advantage of an already unfortunate (and unethical) situation.

What would ensure that the reasons listed above for conducting the trial in a developing country are balanced in a manner that results in an ethical outcome for the host country? Is there enough scientific and public health justification for this, or are the advantages to the manufacturer taking precedence?

13b. Some research is being conducted on attenuated HIV. That is, these vaccines are essentially live virus, which does not cause AIDS but hopefully results in a good immune response. These vaccines have many potential dangers. They may have the potential to mutate into disease-causing virus. They may be capable of being transmitted to other individuals during sexual intercourse or blood transfusion or childbirth. It may be very difficult to determine whether the person becomes truly infected after vaccination. Thus, at this point, it appears that the risk–benefit analysis is too unfavourable to pursue human trials. Is there any issue that should be considered specifically for developing countries in the context of research with these vaccines?

13c. The benefits that might be experienced by individual participants in this trial are difficult to predict. They will receive ongoing monitoring, screening, and counselling. They will also have a

sense of contributing to a solution to an important problem in their country and in the world. It is possible that they will also eventually be assured of an effective preventive strategy for them in the relationship with their partner.

The benefits to the larger community may be perceived as much greater. Even if the vaccine is shown not to be efficacious, the understanding of vaccines will be advanced. In addition, the host country's and the sponsoring country's capacity to carry out a trial such as this will be improved. Finally, there is a chance that an effective vaccine for the country, or maybe the world, will be discovered.

Do the potential benefits to the community justify the many risks to the individual participants that will be encountered in this trial? Are individuals likely to participate in a trial with this risk–benefit profile? Is it fair to ask them to?

ANNEX 2: Workshop Evaluations

Workshop Evaluation, Brazil

There were 17 evaluation forms completed out of 18 non-secretariat participants who were present at the time the evaluation was distributed. The following summarizes the answers given.

Did you feel you were able to understand what was being discussed during the workshops?

Completely	13
Mostly	4
A little	0
Not at all	0

Did you feel that the large group understood your own ideas and opinions?

Completely	2
Mostly	15
A little	0
Not at all	0

Do you feel that the large group is now aware of the ideas and opinions of the community that you represent?

Completely	2
Mostly	15
A little	0
Not at all	0

Do you have any concerns about what the final summary says, and what information will be passed on to the Geneva Conference in June?

No	10
Yes	5
No Answer	2

Please explain

Since Brazil is unique for this side of the world, special consideration should be given to ensure Caribbean concerns and expectations are included.
I cannot try to give a position until I have seen and read the reports from the other workshops, which we will hopefully receive by May 1998.
The limited time frame precludes time to assess this and feedback.
Responsibility of institutional ethics infrastructure, responsibility of continuity of funding support.

I think it is a big responsibility to propose a revision of CIOMS guidelines. I would like to examine carefully the final summary.

What was useful about this workshop for you, and for your community?

The small as well as the large group discussion facilitate in-depth/full discussion as well as learning. Allowed participants to bond on issues, and as a region.
It gave me an opportunity to present the realities of my region and to relay/ be the voice of the community in terms of articulating their needs and mandate if we are to go forward with the vaccine initiative in our region.
To understand more fully the spectrum of developing communities in the region. Also to realize that we all share similar goals and concerns. Good group interaction.
Opinions, exchanges, discussions
Reflection and input to the workshop through local expertise.
The opportunity of discussing very important issues regarding vaccine trials and trying to develop ethical guidelines.
Listening to the opinions of a diversity of developing countries, and individuals' background on ethics and ethical issues involved in clinical trials; precision on what the crucial ethical conflicts are currently arising in HIV study plans.
Offer my comments for community mobilization and participation on vaccine trials...more social control (large information and ethical point view)
All things were very important.
I work in the HIV vaccine cohort and I'd like the follow-up of the seroconversions too. With this opportunity of participating in this workshop, I could talk about our experience and thoughts about this, besides exchanging experiences with the other people and with other regions.
Everything was important because all the issues were very well chosen and relevant. I'll be able to give a lot of information to my community and team and improve the discussion among them.
To improve comprehension and understanding of the issues involved in ethics of vaccine trials getting access to both, or various, sides and positions.
To share ideas from different countries, communities and points of view of persons from divers backgrounds.
Scientific information about current developments of vaccination.
Opportunity to establish communication with people with the same professional (ethical) preoccupations.
I thought it was an extremely useful meeting.

Suggestions for improvement, other comments:

The scenarios were a very good idea. Maybe if they are more simplified, the time we have for discussion would be increased.
Previous distribution of reading material.
More time for plenary discussion, the principal opportunity to know all the different opinions.
Scenarios look unnecessarily sophisticated. It would be better to reduce their elements without becoming simplistic.
Include members from developing countries from other regions, such as Africa and Thailand. Especially community members. Include activists from European countries, like from TRT5-France or EATG.
To receive the scenarios for discussion sometime before the meeting in order to be more prepared for the meeting.
I have no criticism, and the methodology used really made things easier.
To use the language of the majority of the participants.

Send material to participants before meeting.
Write reflections/thoughts before meeting, if possible with specific data already available.
Good conference. Can be improved by circulation of the final report, and also report of similar consultations. Thanks for the trip to Ouro Preto!
At the international meetings there must be representation from ALL countries involved or about to be involved in vaccine trials, since they are the only ones who can truly articulate their needs. All must be present and sit at the decision-making table.
This approach to the development of guidelines allows for more consensus-building internationally. This is a model that should be encouraged.
This process of consultation should be ongoing.
Send us as much data/reports as possible before the meeting to help us prepare.

Workshop Evaluation, Thailand

There were 12 evaluation forms completed out of 13 non-secretariat participants who were present at the time the evaluation was distributed. The following summarizes the answers given.

Did you feel you were able to understand what was being discussed during the workshops?

Completely	5
Mostly	7
A little	0
Not at all	0

Did you feel that the large group understood your own ideas and opinions?

Completely	2
Mostly	9
A little	1
Not at all	0

Do you feel that the large group is now aware of the ideas and opinions of the community that you represent?

Completely	2
Mostly	8
A little	2
Not at all	0

Do you have any concerns about what the final summary says, and what information will be passed on to the Geneva Conference in June?

No	5
Yes	6
No Answer	1

Please explain

The final summary should also be seen/reviewed by companies producing the candidate vaccines

Confident the report will reflect the proceedings.
Would like to look at the revised version following the plenary session in which the group discussed and modified the summary statements.
What is obtained from the workshop may not be the best consensus concerning HIV vaccine studies. More contributions should be explored or welcome from the Geneva Conference.
No concerns after the long process of reviewing the summary statements that was undertaken.
Not enough time to explain here, but generally, the comments that resulted are not systematic.
I'm concerned about the informed consent. The informed consent should be made as clear as possible to the participant of the vaccine trial, and in the very beginning.

What was useful about this workshop for you, and for your community?

To understand complexities related to vaccine trials, ethics, and issues related to the operationalized basic principles of ethics.
I found this workshop very useful for me, for my community, and also for my work.
It was very useful for me as well as for my country because it will complement and improve the guidelines and recommendations for our ethics committee.
Gain new knowledge on vaccine trials (lessons learned from Thailand and other developing countries).
Understand that review and developing a working ethical review committee is needed for our country.
Learn from participants with different expertise and background concerning the ethical considerations of an HIV vaccine study.
The process leading to the discussion of the issues was helpful.
Small group discussions.
Diversity of national and professional background of the participants.
The workshop gave me a better understanding of not only the scientific process involved in a trial but also the psycho-social/ethical dimension.
Learning about the ethical issues and ethical review process.
Contacts made.
Being able to share views with others.
Fantastic exposure to the variety of thinking, similarities, and differences.

Suggestions for improvement, other comments:

Some reservation about the preponderance of Thai representation biasing discussions and results.
It would have been 'easier' had we had somebody who represents a drug company and/or someone with legal background.
Should provide some time to discuss ethical issue on HIV vaccine trial in a general way without being limited to specific scenarios.
Time for discussion in small groups is too short.
Need more participants from social science and communication science and mass media.
More gender balance.
Things seemed rushed at times.
Some people from vaccine development companies should be invited to join this workshop. Otherwise the comment from investigators side will not have any clarification and company point of view is not shared.
The way to draft a scenario of hypothetical HIV vaccine study for discussion of ethical aspects relating to HIV vaccine trials is a good one.
Improvement of case studies to incorporate other issues related to HIV vaccines.

Workshop Evaluation, Uganda

There were nine evaluation forms completed out of 11 non-secretariat participants who were present at the time the evaluation was distributed. The following summarizes the answers given.

Did you feel you were able to understand what was being discussed during the workshops?

Completely	6
Mostly	3
A little	0
Not at all	0

Did you feel that the large group understood your own ideas and opinions?

Completely	3
Mostly	5
A little	1
Not at all	0

Do you feel that the large group is now aware of the ideas and opinions of the community that you represent?

Completely	2
Mostly	3
A little	3
Not at all	1 (no prior consultation with community)

Do you have any concerns about what the final summary says, and what information will be passed on to the Geneva Conference in June?

No	6
Yes	3
No Answer	0

Please explain

Time for summary ran short, and toward the end was rushed
I feel that the ethical guidelines should be looked at more critically, with a view to taking into account the current realities of imbalance; i.e. The poor have a bigger burden, they need the research more.
How is it going to be presented? Is it through a round-table discussion, which I would propose?
There was consensus in the final discussion
I shall not have seen the final summary document. There is a need for participants to append their signatures on the final draft.

What was useful about this workshop for you, and for your community?

Networking with participants
Process of conduct of workshop, small group discussion and plenary scenarios as a basis to raise issues

It was a useful review of most of the ethical issues involved in HIV vaccine trials, and an interesting exchange of perspectives of how trial issues manifest in different populations.
The opportunity to work with African colleagues and learn about the issues, challenges, and problems they have and the cultures and political systems in which they work.
The experience was informative.
The need for preparation before launching trials.
We went through most of the questions that could possibly arise in connection with all three phases of a trial. Above all, I have met many interesting people and learned a lot.
The scenarios and the group work. The plenary sessions were also very useful.
Process design allowed for general discussion as well as country or region- specific issues. The workshop was well facilitated; logistic problems were quickly solved; the hospitality was superb.
Different countries have different priorities, but these countries seem to appreciate what my community has been doing.
I have more understanding of why there are delays to start vaccine trials.
Diversity in approach to scientific and ethical review.
Concurrence about the need of an HIV vaccine ASAP.
Ability of the participants to discuss issues realistically.

Suggestions for improvement, other comments:

It would be appropriate for participants to study the final draft document since this will be used for future presentations and generating consensus towards the development of the UNAIDS guidance document.
One community person from this meeting, if possible, could be invited to the June Geneva meeting.
Action-oriented perspective is needed.
We should not wait for a perfect vaccine while people continue to be infected.
International and regional organizations should get involved to pave the way for immediate vaccine development.
Funding the pharmaceuticals or providing loans may be an important way forward.
The workshop had a huge bias toward basic science. Most of the principles and issues discussed were technically scientific.
It would have been very useful if the background materials were sent to the participants in enough time, say two weeks or a month before the workshop.
I did not fully express myself.
The meeting was very difficult. For instance, I feel that there was not enough time spent on informed consent and the recruitment process.
Further participatory exercise is important.
Had the agenda and background documents been sent ahead of time, the discussion would have been more enjoyable and successful.
Thanks.
More science background and more history of clinical trials at the beginning.
Not very clear where the workshop fits in within the process of developing the final guidelines. Specifically, at which point will country level discussions take place with IRBs? Two products, HIV vaccine research guidelines, and revision of existing — between the two?
Thanks to organizers for a great workshop including excursions and warmth and hospitality.

ANNEX 3: List of Participants

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