

FACT sheet

Ethical Issues Concerning HIV Vaccine Development¹

Why is it important to understand ethical issues?

Developing preventive HIV vaccines requires the involvement of many sectors of society. Researchers, governments, private industry and communities around the world need to contribute if an effective HIV vaccine is to be developed. Yet these various sectors of society have different perspectives and motivations – ethics provides a way to build process, agreement and accountability among them. Ethics are a set of principles that guide behavior. A range of documents have been developed over time to guide ethical practice of research involving human subjects. It is important for communities to be aware of and understand the basic principles that guide ethical research. This will increase their capacity to participate in HIV vaccine research, assess their priorities, and hold researchers and governments accountable to respect ethical research standards.

The role of the community

While developing HIV vaccines requires enormous dedication from many scientists and researchers in addressing the key scientific questions, non-scientific communities have an equally important role to play. Without community participation, development of HIV vaccines would be impossible because vaccine development depends on clinical research of experimental vaccines, tested in people. There is no other way to determine if an experimental vaccine is safe and works. Instead of conducting research on communities, scientists need to conduct research with communities. Also, communities are important advocates as public demand for HIV vaccine research is a necessary and powerful factor to motivate governments to prioritize HIV vaccine development as part of their comprehensive response to AIDS.

Section 1: Basic Principles of Ethical Research

All research involving human subjects should follow current internationally accepted ethical standards. These standards include recognizing the freedom of individuals to decide to take part in a research study, the necessity of maximizing the benefits and minimizing the harms of research, and equitable distribution of the costs and benefits of research.

The Principle of Respect for Autonomy: Respect for Persons

The principle of respect for autonomy promotes the idea that every person is free, independent and has the right to make their own decisions. The principle of respect for autonomy requires researchers to recognize the freedom of individuals to decide if they want to take part in a research study. It also stipulates protections for individuals with reduced autonomy (e.g. underage youth, people with limited mental capacity or marginalized groups). This principle asserts that individuals should not be coerced to

¹ Information contained in this Fact Sheet was sourced from the ICASO publication 'Finding Your Way – A guide to understanding ethical issues related to participation in clinical trials for preventive HIV vaccines'

participate in research; rather, they must make their own informed decisions. One fundamental application of this principle is the requirement of an adequate informed consent process.

The Principles of Beneficence and Non-maleficence

Beneficence means ‘doing good.’ The principle of beneficence states the necessity of maximizing the benefits and minimizing the harms of research. Researchers must act in ways that promote the welfare of research trial participants and others who may benefit in the future from the research. A balance must be struck between any potential benefits of participating in research and any potential risks. In some research, there may be no direct benefit to the participant, and in this kind of research, the potential risks and inconvenience to the participant must be justified by the benefits to society through the knowledge gained during the research.

Risk-Benefit Ratio

Potential risks to volunteers should be identified and minimized, for example through education, empowerment and psychological and legal support. Likewise, potential benefits should be identified and maximized. The risks to individual participants should be outweighed by the benefits to the individual or society.

Examples of Potential Risks

- Expected side-effects due to administering an experimental HIV vaccine (e.g. pain, redness and swelling.)
- Unforeseen side-effects resulting from the experimental vaccine.
- Vaccine induced sero-positivity
- False sense of protection from HIV (the vaccine being studied is experimental and volunteers should understand they are not protected from HIV.)
- Stress of repeated HIV testing throughout the trial.
- Social harms.

Examples of Potential Benefits

- Determining the safety, immunogenicity, and efficacy of a vaccine that, if effective could impact the HIV pandemic.
- Comprehensive HIV risk-reduction counseling.
- Access to prevention resources (condoms and treatment for sexually transmitted infections.)
- Regular contact with counselors.
- Access to HIV treatment should a participant become HIV positive during the course of the trial.

The Principle of Justice

Justice means ‘fairness.’ The principle of justice calls for the equitable distribution of costs and benefits of the research. The benefits and burdens of research must be distributed equally and fairly among all social groups and classes who stand to be affected by the research. The principle of justice mandates that individuals and communities should be invited, or selected, to take part in research according to the scientific goals of the study and not for reasons unrelated to the research (e.g. convenience). Participants who are asked to assume potential risks should have a reasonable likelihood of being beneficiaries of the research. Those who assume the risks and discomforts of research should stand to benefit from the research, and those who stand to benefit should contribute to its risk burdens.

Early Access to HIV Vaccines

Communities that contribute to the development of preventive HIV vaccines should be prioritized for early access to any effective HIV vaccine. Also, communities at high risk of HIV infection should also be prioritized. Access to HIV vaccines should not be limited only to those who can afford to pay for them.

Section 2: The HIV Vaccine Development Process

Developing a Protocol

There is a lot of work that goes into preparing for any clinical trial – especially to ensure that the trial is ethically and scientifically sound. In order for an experimental vaccine to begin clinical testing, a protocol is written. A protocol is a clear and detailed plan of a scientific experiment. It describes the purpose of the study, defines specific study endpoints (the variables to be measured), and explicitly describes every procedure. Before any research study begins, the protocol must be reviewed and approved by an institutional review board or an ethics review committee. These bodies review the protocol and determine if the study design meets the ethical and scientific standards necessary to conduct research in human subjects. If a study protocol does not meet these standards, the research project cannot continue.

Community Advisory Board

A community advisory board (CAB) may also review the protocol to ensure that the research study has been informed by the community in which the study is to take place. CABs are typically made up of members of the community who represent either the community at large and/or the population being recruited into the study. CABs work to ensure that community concerns and priorities are factored into research activities, providing an opportunity for meaningful community participation in HIV vaccine trials. CABs also provide a link between the researchers and the community. If there is not a CAB, another similar mechanism for community consultation on HIV vaccine research should be employed.

Data Safety and Monitoring Board (DSMB)

The trial sponsor will also establish a data safety and monitoring board (DSMB). The DSMB reviews data throughout a trial to ensure the safety of trial participants. If the DSMB sees any indication that the vaccine or placebo is harming volunteers, they will have the research study stopped. Also, if during an efficacy trial the vaccine is clearly effective, the study may be stopped and all volunteers will be provided with the vaccine.

The 6 Stages of HIV Vaccine Trial Participation

For the purpose of this Fact Sheet, HIV vaccine trial participation is broken down into 6 easily recognizable stages, from the point of view of trial volunteers.

The 6 Stages of HIV Vaccine Trial Participation:		
Stage 1	First Contact	This is the first stage of participation, when a potential volunteer hears about an HIV vaccine research trial for the first time.
Stage 2	Informed Consent	The stage when a potential volunteer receives all information and decides if they want to join an HIV vaccine research trial.
Stage 3	Screening	The stage when a volunteer's eligibility to participate in a trial is assessed through a screening process.
Stage 4	The Trial	The stage when the HIV vaccine research activities are conducted.
Stage 5	End of the Trial and Results	The stage when the HIV vaccine research trial ends and the trial results are announced.
Stage 6	After Efficacy	The stage after an experimental HIV vaccine is shown to be effective.

At any time during the clinical trial process, volunteers can choose to end their participation without fear of losing the benefits that they would be entitled to otherwise. This is critical and should be made absolutely clear to volunteers from the start.

Stage 1: First Contact

This stage in the vaccine development process represents the first time you may hear about an HIV vaccine clinical trial. This may be the first time you have ever heard of HIV vaccine research; it may be the first time you have ever heard of HIV or AIDS.

Typically, two things will happen at this time: 1) community educators, trial recruiters and outreach staff from the trial will work to raise awareness of the HIV vaccine research being conducted in the community; and 2) they will identify people who might be interested in volunteering for a clinical trial. They may be looking for volunteers for a specific HIV vaccine clinical trial currently underway, or they may want to create a pool of individuals for future vaccine clinical trials. Usually a community educator, recruiter or outreach worker will be available to talk about HIV vaccine research, how clinical trials work, and provide information about trials currently underway or starting soon. They should be able to answer any questions you have.

In order to get more information about volunteering, you will probably have to meet with research staff at a clinic. Here you will go through two important processes: the informed consent process and the screening process. These processes may happen at the same time or one after the other, but both must be completed before anyone can join a clinical trial.

Why do you want to volunteer?

You should think about what is motivating you to volunteer to be a part of the trial. Is it because you have friends or family who have been affected by HIV? Or is it because the trial offers benefits that you desire? Having a good understanding of what motivates you will be important to keep in mind as you learn more about HIV vaccine research.

Social Harm

One concern to be aware of is social harm – the experience of social discrimination or hardships resulting from being associated with the vaccine research. Will people assume you have HIV if you join the trial? Will your family or friends treat you differently if they find out you are part of an HIV vaccine trial? These are important questions to think about.

Expectations

It is important to monitor your own expectations of participating in an HIV vaccine trial, and communicate them to the research staff. There is no guarantee that you will be protected from HIV if you participate in a trial. You should also be aware that the product being tested in the trial may not end up being an effective vaccine. Also, it is important to remember that making an HIV vaccine will take many years. Be aware of your expectations and make sure they are realistic so that you are not disappointed at the end of the trial.

Stage 2: Informed Consent

In order to follow the guidelines for ethical human subject research, extra steps must be taken to make sure you truly understand what it means to volunteer for a clinical trial and that you truly agree to participate. This process is called informed consent. Informed consent is a process to ensure that individual autonomy is respected and volunteers are not put in unnecessary danger without their knowledge. This process is required of all research involving human subjects.

It is important to know that informed consent is not just signing a piece of paper that says you have been informed of and understand what you are volunteering for. It is an ongoing process throughout the trial of learning about the research and deciding whether to continue volunteering. Any new information about the research should be provided to all trial participants as soon as possible. Information about the clinical trial should be provided in a way and in languages that are easy for you to understand.

The informed consent process should explain:

- the rationale for the study.
- the nature of the experimental vaccine.
- any possible side effects of the vaccine.
- unknown outcomes – there is no guarantee that the HIV vaccine being tested will offer any protection against HIV infection.
- design or methodology (use of placebo and randomization.)
- practical aspects involved in personal participation, the kinds of procedures and tests that participants will undergo.
- the potential risks and expected benefits of participation.
- the personal implications of participation in the study, e.g. the stress of repeated HIV testing.
- the confidentiality to be expected, and any limits to it.
- the freedom to withdraw at any time.

Those who may have a limited ability to provide informed consent should not be excluded from participating in HIV vaccine trials entirely. In fact, UNAIDS makes specific recommendations about working with populations that may have limited freedom or capacity to provide informed consent.

Joining Other HIV Vaccine Trials

You should know that once you have participated in an HIV vaccine clinical trial, you may no longer be eligible to join another trial in the future. This is because researchers will want to ensure that anything they observe during a trial is related to the vaccine being studied – not to another experimental vaccine you may have received earlier.

Future HIV Vaccines

There is a risk that by participating in this clinical trial, other future vaccines for HIV may be less effective or not effective for you. It is important that you weigh your options carefully and make the decision that is right for you.

Stage 3: Screening

The informed consent and screening processes can happen at the same time, or consecutively – it will be different for each trial. However, it is important to know that both activities must be completed before a volunteer can join a trial. Just because a volunteer has agreed to participate in a clinical trial does not mean they will automatically be enrolled in the trial. Anyone who volunteers to be part of a clinical trial must go through a screening process to make sure they are eligible to participate.

Vaccine Induced Sero-positivity

Experimental HIV vaccines that stimulate the production of antibodies may cause a person to test positive on a standard ELISA test. This does not mean that you have HIV, just that you have antibodies to HIV. It is possible to tell the difference between vaccine-induced antibodies and actual HIV infection. You will be asked to have all of your HIV testing done at the trial site to minimize confusion about your HIV status. If you do have long lasting antibodies from the vaccine trial, the researchers should provide you with HIV testing for as long as you need it. The staff at your trial site should help you if there is any question about your HIV status because of vaccine induced sero-positivity.

Cultural Sensitivity

The informed consent process may be well recognized in health research, but HIV vaccine trials are being conducted within cultures that may have differing views about health and decision making. There are steps that can be taken to incorporate local traditions and practices into the informed consent process. It is important to use language and concepts that are appropriate for the local culture and social context. However, cultural sensitivity does not mean unquestioning acceptance of cultural norms that might conflict with international standards for consent. It is important not to ignore ethical protections in the name of respect for local culture. In research with cultures that require men to make decisions for women, respect for the autonomy of women as individuals cannot be ignored completely out of respect for culture. Efforts to find a mutually acceptable mechanism for obtaining consent should be explored.

The screening process involves medical tests and interviews. Medical tests including blood draws, an HIV test, a pregnancy test and a general physical examination are used to determine if you are in good health. This is important because researchers need to make sure you are not put in unnecessary danger, honoring the principle of non-maleficence. Also, researchers will want to ensure that any adverse reactions or health problems you might experience during the study are directly related to the vaccine, and not from a pre-existing health condition you may have. The interviewers will ask questions about medical history, health and lifestyle. Some of the questions may feel very personal to you, including the topics of sexual behavior and drug use, but it is important that you provide accurate information. As information about your lifestyle and health are collected, it is compared to a list of inclusion and exclusion criteria. These are criteria researchers use to determine if someone is eligible to participate in the clinical trial. Exclusion criteria are characteristics that will exclude a volunteer from enrollment.

After completing the screening process, you will meet with study staff to learn about the results of your tests and your eligibility to participate in the trial. If you meet the eligibility requirements, and you have gone through the informed consent process, you can then be enrolled in the study.

Confidentiality

A lot of information about a volunteer is collected as part of participation in HIV vaccine research. Very personal information, like sexual behavior, drug use, HIV status, medical conditions or even association with the trial could be harmful if the wrong people discover it. It is important that the researchers commit to and explain how they will keep personal information confidential. Researchers should clearly explain any limitations to their ability to keep information confidential.

HIV Testing

Trial volunteers must be HIV negative and the screening process will include an HIV test. Do you understand what it means to be infected with HIV? Are you ready to learn your HIV status? What will happen if you test positive? Do you have adequate resources (including treatment, care and social support) available to you? You should receive HIV counseling as part of being tested for HIV, so you can learn about how to protect yourself, what to do if you do test HIV positive and where you can get help.

Stage 4: The Trial

Once you have given your informed consent to participate in the trial, and the screening process shows that you are eligible to volunteer, you can be enrolled in the study. Once enrolled in the trial, you will have your first study visit. Your first visit will involve a set of medical tests, including another HIV test and a pregnancy test for women. These tests will check to make sure your health status has not changed since you went through the screening process. Some researchers will ask for a sample of your blood for later research. You may be asked to stay for an extended period of time after your first visit to the clinic. This way the research staff can observe you carefully for any side effects. You may also be asked to keep a diary of your health for the first few days.

Researchers should provide you with counseling every time they give you an HIV test, and you should receive comprehensive risk-reduction counseling and access to prevention methods every time you attend the clinic. It is critical that trial volunteers understand that the vaccine being studied is experimental and there is no guarantee of protection.

Most HIV vaccine trials are designed to be double-blind, placebo-controlled trials. At the first visit you will receive your first injection, of either the vaccine being tested or the placebo. A placebo is an inactive substance administered to some study participants while others receive the experimental vaccine, to provide a basis for comparison of effects. Scientists use the placebo to compare the effects of using an experimental vaccine to using no vaccine. Placebo-controlled means that volunteers are divided into at least two groups. The groups will have a similar number of men and

women, people of various ethnicities and age ranges, etc. One group will get the experimental vaccine, while the other one will get a placebo. The group that receives the placebo is called the control group. In some cases, the control group may get something besides a placebo – such as another vaccine. Later, at the end of the trial, researchers will compare the two groups to determine the safety, immunogenicity or efficacy of the vaccine. Double-blind means that neither the trial volunteers, nor the researchers will know who is getting the vaccine and who is getting the placebo. This makes the reporting and collection of data more objective, since no one knows who got the vaccine. Unblinding occurs after all data has been collected and analyzed.

Trial volunteers may end their participation before the trial is complete. This can happen for a variety of reasons such as:

Side Effects – If you have a serious side effect during the trial, your participation may be ended.

High Efficacy – If preliminary results from a trial show high vaccine efficacy, the trial could be stopped so that all trial participants can receive the vaccine.

Missed Study Visits – If you miss too many visits or delay a visit for too long, you may no longer be eligible to continue volunteering for the trial.

Becoming Infected with HIV During the Trial – If you become infected with HIV during the course of the trial, you will no longer be eligible to participate. The trial sponsors may have committed to providing AIDS treatments to volunteers who become infected during the trial. Some researchers may ask you to continue coming to the site so they can see if the vaccine has any effect on the progression of HIV disease.

Deciding to Drop Out – You have the right to stop volunteering for any reason at any time during the trial. Whatever the reason, you should not have to worry about losing services that you would normally be entitled to just because you choose not to participate anymore.

Stage 5: End of the Trial and Results

After you attend your final visit, take your final set of medical tests and answer your last set of interview questions, your formal participation in the trial comes to an end. All trial participants should be provided with the trial results and be given an opportunity to ask questions about them. However, it may take some time before you learn what the results of the trial are. You should be given some indication of when the researchers expect to announce their trial results. When the trial results are announced, you should also be able to find out if you received the placebo or the vaccine.

Just because a trial shows a product is not efficacious, it does not mean that your participation in the research was wasted. Important information about the vaccine, the immune system and HIV will have been learned because of your participation. If the vaccine is shown to be efficacious, this is great news, but the time for full celebration is yet to come. The success of any preventive HIV vaccine depends on more than just making it – it also must be effectively distributed and used.

Stage 6: After Efficacy

The only way any effective HIV vaccine will actually be able to slow down the global pandemic is if the vaccine is available and accessible to the people who need it most. Many actions can be taken in advance to ensure this. Advocates and policymakers are already beginning to think about how these challenges can be overcome. As they do, they must also consider the amounts of time, resources and political capital needed to invest in the access issue, when a safe and effective HIV vaccine may still be at least a decade away. This is necessary as developing countries still wait an average of 20 years after a vaccine is licensed in industrialized countries before it starts reaching their populations.

Licensing

Before any vaccine becomes available to the public, the makers of the vaccine must apply for a license. National regulatory agencies review data from clinical research and determine if the vaccine is safe and effective. Accelerated licensing has been possible for other products in the past, such as early AIDS treatments.

Manufacturing

Making sure there is enough manufacturing capacity to produce enough vaccine for the world will take time. Building this capacity should be planned well in advance of product licensing.

Purchasing

Historically, it has taken much longer for vaccines for other diseases licensed in industrialized countries to become available in developing countries. Policy makers and advocates have been working on developing novel ideas for purchasing schemes and government incentives, but much more energy must be placed on these efforts while the vaccines are developed.

Distribution/Access

Systems must be developed to prioritize who should get the first batches of HIV vaccine. Distribution of effective HIV vaccines will be greatly improved if governments work now to distribute currently available vaccines for other diseases. The infrastructure established to deliver these other vaccines will provide the necessary infrastructure needed later to distribute HIV vaccines.

From Efficacy Trial to Licensing

It is important to know that proof of efficacy in a single phase III trial does not necessarily mean that a preventive HIV vaccine will be licensed immediately afterwards. There may need to be other trials to gather enough data to get the vaccine licensed.

Post-licensing Trials

Once a preventive HIV vaccine is licensed, it does not mean that the research process is over. Additional trials that happen after a vaccine has been licensed are called post-licensing or post-marketing trials; they study things like long term effects of the vaccine, changes in dosing or administration of the vaccine and other similar topics.