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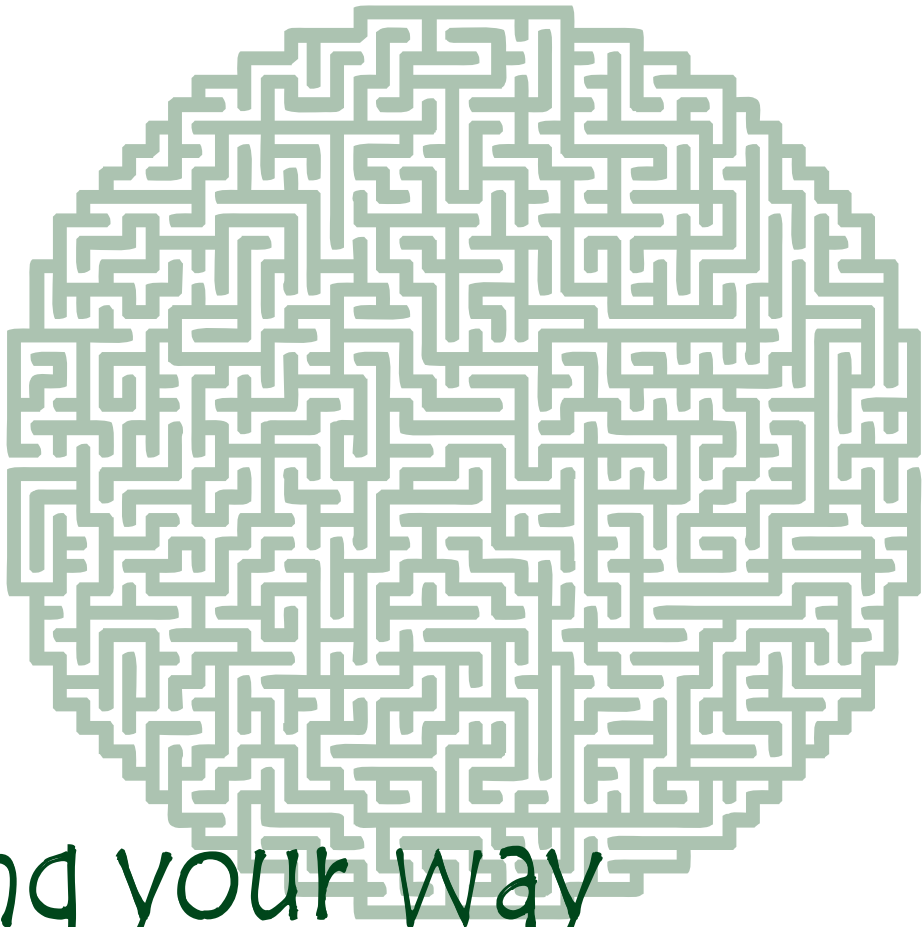

Finding your way

A guide to understanding ethical issues related to participation in clinical trials for preventive HIV vaccines

Finding Your Way: A guide to understanding ethical issues related to participation in clinical trials for preventive HIV vaccines

July 2005
Prepared by Edd Lee

Further copies of this document can be downloaded at:

- www.icaso.org
- www.avac.org

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This is a joint initiative of:

AVAC

Founded in 1995, the AIDS Vaccine Advocacy Coalition (AVAC) is a non-profit organization that uses education, policy analysis and advocacy to accelerate the ethical development and global delivery of vaccines against HIV/AIDS. AVAC works specifically in four critical areas to accelerate AIDS vaccine development: policy formulation, community engagement, evidence-based advocacy and building a global coalition.

ICASO

ICASO, the International Council of AIDS Service Organizations, works to strengthen the community-based response to HIV/AIDS by connecting and representing NGOs throughout the world. Founded in 1991, ICASO operates from Regional Secretariats based on all five continents, guided by a secretariat in Toronto, Canada.

We gratefully acknowledge contributions from colleagues who generously accepted to peer review this document: Camille Massey, Ruth Macklin, Shaun Mellors, Stephanie Nixon, Mary Ann Torres, Steve Wakefield, and Mitchell Warren. We are also grateful to Tim Thomas for reviewing and editing various drafts of this report.

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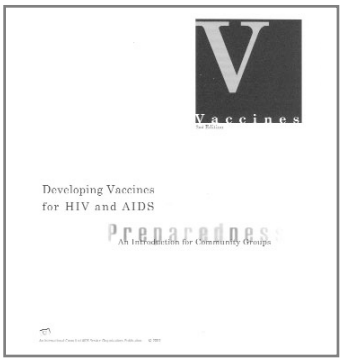
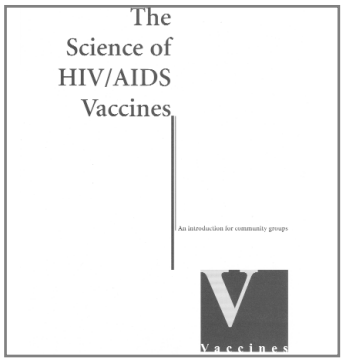
INTRODUCTION

WELCOME!

You are about to begin a journey through the very important and complex world of research — research to make a preventive vaccine for HIV.

There are many questions to answer along this journey. Some are questions of science. Others are questions of public policy. And some are questions of **ethics**. This guide is designed to help you gain a better understanding of the ethical issues involved in developing preventive HIV vaccines. With the information provided in this guide you should be prepared to find your own way of participating in preventive HIV vaccine research and development.





This guide is part of ICASO's series of HIV vaccine primers for communities. Other primers in the series address HIV vaccine science and community involvement, and they are listed at the end of this document in the resource section, page 29.

THE PURPOSE OF THIS GUIDE

This guide will provide you with an introduction to the ethical principles raised in preventive HIV vaccine research and development, and examples of some of the actions taken to honor those principles.

The goals of this guide are to:

- Introduce you to the basic principles of ethical human subject research;
- Highlight critical ethical issues that clinical trial volunteers may face in preventive HIV vaccine research and development;
- Provide a starting point for community dialogue about ethics and HIV vaccine research and development; and
- Serve as a reference for other useful information about ethics and HIV vaccine research and development.

This guide is not designed to provide you with solutions to ethical issues raised in HIV vaccine research and development. It is important to take into consideration the specific details of any given trial, trial site, trial sponsor, community or country involved in your situation. There are other excellent resources that can provide additional information on related topics, and they are included in the resource section at the end.

WHO SHOULD READ THIS GUIDE

While much of this guide is intended for a prospective clinical trial volunteer, it provides a useful introduction for anyone who wants to learn about ethical issues and HIV vaccine development. This guide is particularly useful for people who are considering joining a clinical trial, community advisory board (CAB) members, community-based organizations, non-governmental organizations (NGOs), HIV/AIDS service organizations, advocates, activists and policy makers.

HOW TO USE THIS GUIDE

This guide is broken into four sections:

SECTION 1 Basic Principles

Basic Principles of Ethical Human Subject Research

This section introduces the basic **principles of ethical research** involving human subjects. These principles provide a framework for addressing various ethical questions raised in HIV vaccine research and development. A greater understanding of these principles is critical to increasing the ability of trial participants, community groups, vaccine advocates and policy makers to contribute to the development of HIV vaccines.

SECTION 2 Vaccine Development

The HIV Vaccine Development Process

This section describes the process for testing preventive HIV vaccines from the perspective of clinical trial participants. For the purpose of this guide, participation in preventive HIV vaccine trials is broken down into 6 stages. At each stage, common ethical issues that clinical trial participants may face are highlighted and explored.

SECTION 3 More Resources

More Resources

This section lists other useful sources of information related to ethical considerations in preventive HIV vaccine development. In addition to documents, websites, and publications, a list of HIV vaccine related organizations with contact information is provided.

SECTION 4 Glossary

Glossary

This section provides definitions of key terms found in the guide. Words found in the glossary are printed in **bold** throughout.

NOTES:

Text boxes

Two types of text boxes are used in this guide to introduce specific concepts and provide important perspectives:

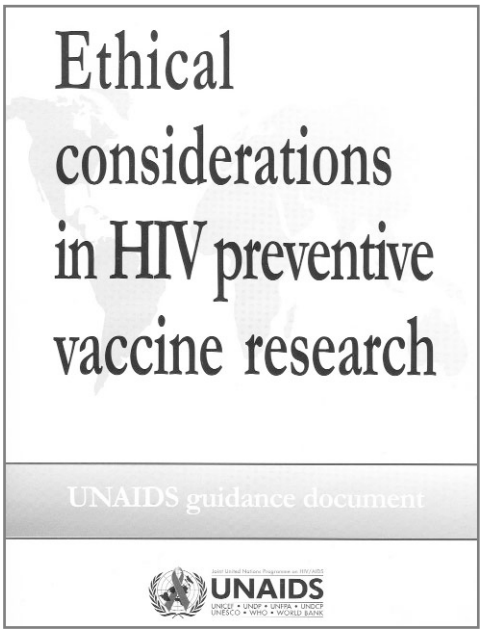
"UNAIDS Guidance Points" boxes

UNAIDS Guidance Point

The Joint United Nations Programme on HIV/AIDS (UNAIDS) convened a series of meetings from 1997 to 1999 involving 33 countries, doctors, lawyers, activists, social scientists, vaccine scientists, epidemiologists, ethicists, representatives of NGOs, people living with HIV/AIDS, and people working in health policy. The goals of the meetings were to:

1. identify and discuss ethical elements specific to the development of preventive HIV vaccines;
2. reach consensus when possible, or identify differing positions when not;
3. increase the ability to address these matters during pending or proposed HIV vaccine research.

The document that resulted from these meetings is titled *Ethical considerations in HIV preventive vaccine research*, and it is based on 18 guidance points to be followed when considering critical elements of HIV vaccine development activities. These guidance points are referenced throughout this guide.



Reproduced by permission of UNAIDS, the Joint United Nations Programme on HIV/AIDS

"Things to Think About" boxes

Things to Think About

These boxes introduce important topics related to HIV vaccine development and ethics.

WHY DO WE NEED PREVENTIVE HIV VACCINES?

HIV/AIDS is one of the greatest public health emergencies the human race has ever encountered. The spread of HIV around the world continues to outpace the global response despite increased funding and political commitments. No region of the world has been spared, and for many countries HIV related illness is the leading cause of death.

In 2004, almost five million people became newly infected with HIV and almost three million lives were lost to AIDS. Now over 20 million people have died since the first cases of AIDS were identified in 1981, and 14,000 men, women and children are newly infected every day. Currently available HIV prevention interventions are effective, but they are not making a big enough impact on the spread of HIV, especially in developing countries.

Social stigma associated with HIV, and inadequate public health systems severely impede the availability and delivery of effective interventions such as prevention education, risk-reduction counseling, condom distribution and needle exchange programs.

UNAIDS Guidance Point 1

HIV Vaccines Development

Given the severity of the HIV/AIDS pandemic in human, public health, social and economic terms, sufficient capacity and incentives should be developed to foster the early and ethical development of effective vaccines, both from the point of view of countries where HIV vaccine trials may be held, and from the point of view of sponsors of HIV vaccine trials. Donor countries and relevant international organizations should join with these stakeholders to promote such vaccine development.

At the same time, the number of people living with HIV/AIDS continues to grow — now close to 40 million people worldwide. While advancements in AIDS treatments have extended the lives of people living with HIV/AIDS, they do not lead to a cure. Tragically, AIDS treatments are still not readily affordable or accessible for the vast majority of people living with HIV/AIDS — especially people in developing countries and from marginalized communities.

The combination of these factors makes for an ethical imperative to develop, as quickly as possible, globally effective vaccines to prevent HIV/AIDS. Any preventive vaccine for HIV should complement other prevention and treatment strategies as part of a comprehensive response to the epidemic.

Historically, preventive vaccines have been extremely powerful and cost-effective for reducing the spread of infectious diseases in both industrialized and developing countries. An effective preventive HIV vaccine could significantly reduce the spread of HIV around the world.

A **vaccine** is a substance that stimulates an immune response. The best possible vaccine for HIV would provide **sterilizing immunity** — i.e. prevent HIV infection altogether. However, HIV has proved to be a significant challenge and many scientists are not sure if development of this kind of vaccine is possible.

Meanwhile, other types of vaccines are also being developed. Some might not prevent infection, but would instead **modulate disease** — i.e. change the progression of HIV related diseases. While these types of vaccines might not prevent HIV infection, they would prevent or delay the onset of disease. Still,

other vaccines may simply reduce a person's infectiousness — or make it much harder for a person living with HIV to infect someone else. All of these kinds of vaccines could be powerful tools in the fight against AIDS.

WHY IS IT IMPORTANT TO UNDERSTAND ETHICAL ISSUES?

HIV/AIDS involves unique biological, social and geographical factors that affect the balance of risks and benefits for individuals and communities participating in HIV vaccine development activities. These factors may require additional efforts to address the needs of those involved, such as:

- An effective preventive HIV vaccine;
- Protection of their rights;
- Promotion of their welfare in relation to HIV vaccine development activities; and
- Full and equal participation.

UNAIDS Guidance Point 3

CAPACITY BUILDING

Strategies should be implemented to build capacity in host countries and communities so that they can practice meaningful self-determination in vaccine development, can ensure the scientific and ethical conduct of vaccine development, and can function as equal partners with sponsors and others in a collaborative process.

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.

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.

UNAIDS Guidance Point 5

COMMUNITY PARTICIPATION

To ensure the ethical and scientific quality of proposed research, its relevance to the affected community, and its acceptance by the affected community, community representatives should be involved in an early and sustained manner in the design, development, implementation, and distribution of results of HIV vaccine research.

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. It has been said that community involvement is research ethics in action. That is because ethical research requires communities to be given open opportunity to meaningfully contribute to the research process.

Further, public demand for HIV vaccine research is a necessary and powerful factor to motivate governments to priori-

tize HIV vaccine development as part of their comprehensive response to HIV/AIDS. 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. Without volunteers from communities willing to roll up their sleeves and take part in clinical trials, no effective HIV vaccine will ever be developed for anyone.

NOTES:

SECTION 1
Basic Principles

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.

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. The discovery of Nazi research atrocities committed during World War II was the impetus for developing research guidelines and in response, the Nuremberg Code was established in 1947. In 1964, the Declaration of Helsinki was adopted by the 18th World Medical Assembly, the first set of recommendations guiding biomedical research involving human subjects. In the U.S., the Belmont Report written in 1979 provides the basis of present day regulations for conducting research involving human subjects. Three key concepts of ethical human subject research are: Respect for persons, Beneficence/Non-Maleficence, and Justice.

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 participate in research; rather, they must make their own informed decisions.

NOTES:

Things to Think About

Vulnerable Populations

In order to test if a vaccine works, large numbers of individuals at high risk for HIV infection must be recruited for clinical trials. The same factors that put these individuals at high risk for HIV infection are also reasons to ensure protection of their rights during their participation in vaccine trials. Examples of populations that may have an increased vulnerability include women, youth, gay/bisexual men, drug users, sex workers, the poor, the homeless, and communities from developing countries.

UNAIDS Guidance Point 7

VULNERABLE POPULATIONS

Where relevant, the research protocol should describe the social contexts of a proposed research population (country or community) or increased vulnerability among potential research participants, as well as the steps that will be taken to overcome these and protect the dignity, safety, and welfare of the participants.that create conditions for possible exploitation .

One fundamental application of this principle is the requirement of an adequate **informed consent** process. Informed consent refers to a person's right to choose whether they will participate in a research trial based on an understanding of all relevant information. Informed consent must be given voluntarily, or free of substantial controlling influence by others. For more information on informed consent, see page 15.

Things to Think About

Special Populations

In the past, some populations have been excluded from participating in clinical research altogether - particularly women and children. UNAIDS has made recommendations about the inclusion of these populations in HIV vaccine research to address specific ethical issues related to working with women and children.

UNAIDS Guidance Point 17

Women

As women, including those who are potentially pregnant, pregnant, or breastfeeding, should be recipients of future HIV preventive vaccines, women should be included in clinical trials in order to verify safety, immunogenicity, and efficacy from their standpoint. During such research, women should receive adequate information to make informed choices about risks to their fetus or breast-fed infant, where applicable.

UNAIDS Guidance Point 18

Children

As children should be recipients of future HIV preventive vaccines, children should be included in clinical trials in order to verify safety, immunogenicity, and efficacy from their standpoint. Efforts should be taken to design vaccine development programmes that address the particular ethical and legal considerations relevant for children, and safeguard their rights and welfare during participation.

Example: The 1932-1972 Tuskegee syphilis study in the United States is often referred to as one of the greatest failures of medical ethics. This study involved mostly illiterate African-American sharecroppers who had syphilis. While trial volunteers were told they were in the study to receive treatment, the study's actual purpose was to observe what happens when the infection goes untreated. This clear violation of the principle of autonomy misled volunteers. As a result, many died even though an effective treatment had been discovered in 1947, and many African Americans still distrust medical research today.

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. In general, research should be done only if the risks to the individual participant are outweighed by the benefits to the participant and society.

SECTION 1
Basic Principles

Things to Think About

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	Examples of Potential Benefits
• 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**	• 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

UNAIDS Guidance Point 9

Potential Harms

The nature, magnitude, and probability of all potential harms resulting from participation in an HIV preventive vaccine trial should be specified in the research protocol as fully as can be reasonably done, as well as the modalities by which to address these, including provision for the highest level of care to participants who experience adverse reactions to the vaccine, compensations for injury related to the research, and referral to psycho-social and legal support, as necessary.

UNAIDS Guidance Point 10

Benefits

The research protocol should outline the benefits that persons participating in HIV preventive vaccine trials should experience as a result of their participation. Care should be taken so that these are not presented in a way that unduly influences freedom of choice in participation.

Non-maleficence means 'not doing harm.' The **principle of non-maleficence** poses an obligation for researchers to never deliberately harm or injure others, and to minimize the risks and inconveniences to trial participants.

Things to Think About

Access to Treatment and Care

For most developing countries, AIDS treatment and care are not readily available to people living with HIV/AIDS. Yet many HIV vaccine research trials will need to be conducted in developing countries, where HIV incidence rates are high. This improves scientists' ability to test a vaccine's effectiveness.

Many have argued that volunteers who take part in vaccine trials should be provided access to AIDS treatment and care if they become infected with HIV during the trial. Yet others suggest that offering AIDS treatment and care as part of volunteering for a trial in countries where treatments are not currently available may cause people to volunteer for a trial, which they may not have done otherwise **(coercion)**. This is a complex ethical area that continues to be debated among government agencies, trial sponsors, product developers, advocates and communities.

UNAIDS Guidance Point 16

CARE AND TREATMENT

Care and treatment for HIV/AIDS and its associated complications should be provided to participants in HIV preventive vaccine trials, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country in light of the circumstances listed below. A comprehensive care package should be agreed upon through a host/community/sponsor dialogue which reaches consensus prior to initiation of a trial, taking into consideration the following:

- **level of care and treatment available in the sponsor country**
- **highest level of care available in the host country**
- **highest level of treatment available in the host country, including the availability of antiretroviral therapy outside the research context in the host country**
- **availability of infrastructure to provide care and treatment in the context of research**
- **potential duration and sustainability of care and treatment for the trial participant**

Ethical and scientific review of proposed research is one important way to ensure that the principles of beneficence and non-maleficence are respected. Ethical and scientific reviewers should not allow research to begin unless the potential benefits of the research outweigh the potential risks to trial volunteers.

Example: While developing the capacity to run clinical trials of preventive HIV vaccines in Kericho, Kenya, the United States Military HIV Research Project (USMHRP) has also worked to develop capacity to prevent mother-to-child transmission of HIV. By maximizing opportunities to address community needs in Kericho, the USMHRP has gained the trust and support of the local communities and businesses.

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. This is also known as distributive justice.

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.

An injustice can occur when a burden is unfairly imposed, or when a benefit is unfairly denied. A burden is unfairly imposed when a group of persons is selected to bear more than its fair share of the burdens of research participation, or when a group of persons (e.g. the poor) are chosen to bear the burdens of research so that others (e.g. the wealthy) can benefit from the new knowledge or products.

Things to Think About

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.

UNAIDS Guidance Point 2

VACCINE AVAILABILITY

Any HIV preventive vaccine demonstrated to be safe and effective, as well as other knowledge and benefits resulting from HIV vaccine research, should be made available as soon as possible to all participants in the trials in which it was tested, as well as to other populations at high risk of HIV infection. Plans should be developed at the initial stages of HIV vaccine development to ensure such availability.

Example: When penicillin was discovered to treat syphilis in 1947, justice would have required the Tuskegee syphilis study provide treatment to all trial volunteers and end the study. Instead study volunteers were allowed to die untreated, never receiving the benefits of medical research even though they contributed themselves.

NOTES:

Notes:

THE HIV VACCINE DEVELOPMENT PROCESS

The Research Process: The development of HIV vaccines is an expensive, long and complex process. There are many ways to explain this process. Many view the process through the lens of scientific discovery, starting with basic science and pre-clinical research, or research that occurs in the laboratory, before testing in human beings begins. This is followed by clinical research, or research that involves human beings. Afterwards the process focuses on licensing, manufacturing, purchasing and distribution of effective HIV vaccines. More information can be found in the ICASO primer: The Science of HIV/AIDS Vaccines: An Introduction for Community Groups.

Following are the steps involved in the basic science and pre-clinical vaccine development process:

1. Development of Concept:	The initial idea of a vaccine is developed. Scientists develop a hypothesis (or an educated guess) of how to stimulate an immune response that will prevent HIV infection, transmission or disease progression. If a concept seems promising, it is moved into laboratory testing.
2. Laboratory Testing:	New concepts are developed into experimental vaccines. These experimental vaccines are studied in test tubes to determine their potential for stimulating a desired effect on the immune system. If the experimental vaccine shows promise at this stage, it moves into animal testing.
3. Animal Testing:	Experimental vaccines are tested for the first time in living creatures. Small animals are generally used to test for safety and tolerability, while non-human primates are used to predict how well the experimental vaccine works. If the experimental vaccine is promising in animal testing, clinical research begins.

Not all products will go from pre-clinical development into clinical research. If a product does move forward, then the clinical research process is as follows:

Phase I

- These are the smallest trials, generally involving fewer than 100 trial volunteers who are at low risk of becoming infected.
- These trials primarily test for the safety and tolerability of the experimental vaccine.
- These trials generally last 12 to 18 months.
- These trials are often the first time the product has been tested in humans.

Once the experimental vaccine is shown to be safe and tolerable, it moves into phase II testing.

Phase II	• These trials generally involve hundreds of trial volunteers. • These trials test for safety, tolerability and immuno genicity (the vaccine's ability to stimulate an immune response). • These trials can last up to 2 years.	If the experimental vaccine is shown to be immunogenic, and is still safe and tolerable, it may move into Phase III testing.
Phase III	• These are the largest trials — generally involving thousands (or tens of thousands) of trial volunteers who are at higher risk of HIV infection. • These trials test for safety, tolerability and efficacy (the vaccine's ability to prevent HIV infection, trans mission, or disease progression). • These trials generally last 3 to 4 years.	If the experimental vaccine is shown to have efficacy, the product must then be licensed, manufactured, purchased and distributed. (These elements of "access and use" should not wait for the completion of Phase III trials as this will delay the process of getting the product actually used. Access plans should be formulated as part of the research and development process.)

Things to Think About

Phase IIB Trials or Proof of Concept Trials

Recently HIV vaccine researchers have been designing trials that fall somewhere between phase II and phase III - called phase IIB trials, or proof of concept trials. Phase IIB trials may provide an indication of an experimental vaccine's efficacy but are less costly in terms of money, time and number of volunteers. However, phase IIB trials are not designed to provide a useable vaccine at the end of the trial - instead these trials test the general concept of the vaccine. Eventually, a phase III trial would have to be conducted to develop a useable and licensable HIV vaccine.

UNAIDS Guidance Point 8

Clinical Trial Phases

As phases I, II, III in the clinical development of a preventive vaccine all have their own particular scientific requirements and specific ethical challenges, the choice of study populations for each trial phase should be justified in advance in scientific and ethical terms in all cases, regardless of where the study population is found. Generally, early clinical phases of HIV vaccine research should be conducted in communities that are less vulnerable to harm or exploitation, usually within the sponsor country. However, countries may choose, for valid scientific and public health reasons, to conduct any phase within their populations, if they are able to ensure sufficient scientific infrastructure and sufficient ethical safeguards.

Developing a Research 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.

UNAIDS Guidance Point 4

Research Protocols and Study Populations

In order to conduct HIV vaccine research in an ethically acceptable manner, the research protocol should be scientifically appropriate, and the desired outcome of the proposed research should potentially benefit the population from which research participants are drawn.

Development of a protocol helps to facilitate standardization of clinical trial conduct, because it guides all investigators across sites and allows comparative analyses from study to study. It also allows others to assess what the researchers are doing. A protocol provides a foundation for consistency of data interpretation, and serves as a roadmap and reference guide for the clinical trial.

While there is no required format for a protocol, the *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use* lists guidelines for components of a protocol.

A study protocol should include:

- title page
- table of contents
- protocol summary
- purpose and trial objectives
- background
- trial design
- statistics
- quality assurance and control
- ethics
- additional documents, such as informed consent materials and protocol amendments

UNAIDS Guidance Point 6

Scientific and Ethical Review

HIV preventive vaccine trials should only be carried out in countries and communities that have the capacity to conduct appropriate independent and competent scientific and ethical review.

Before any research study begins, the protocol must be reviewed and approved by an **institutional review board** or an **ethics review committee**. These bodies read through 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.

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.

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.

Things to Think About

Choosing not to participate

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.

The 6 Stages of HIV Vaccine Trial Participation

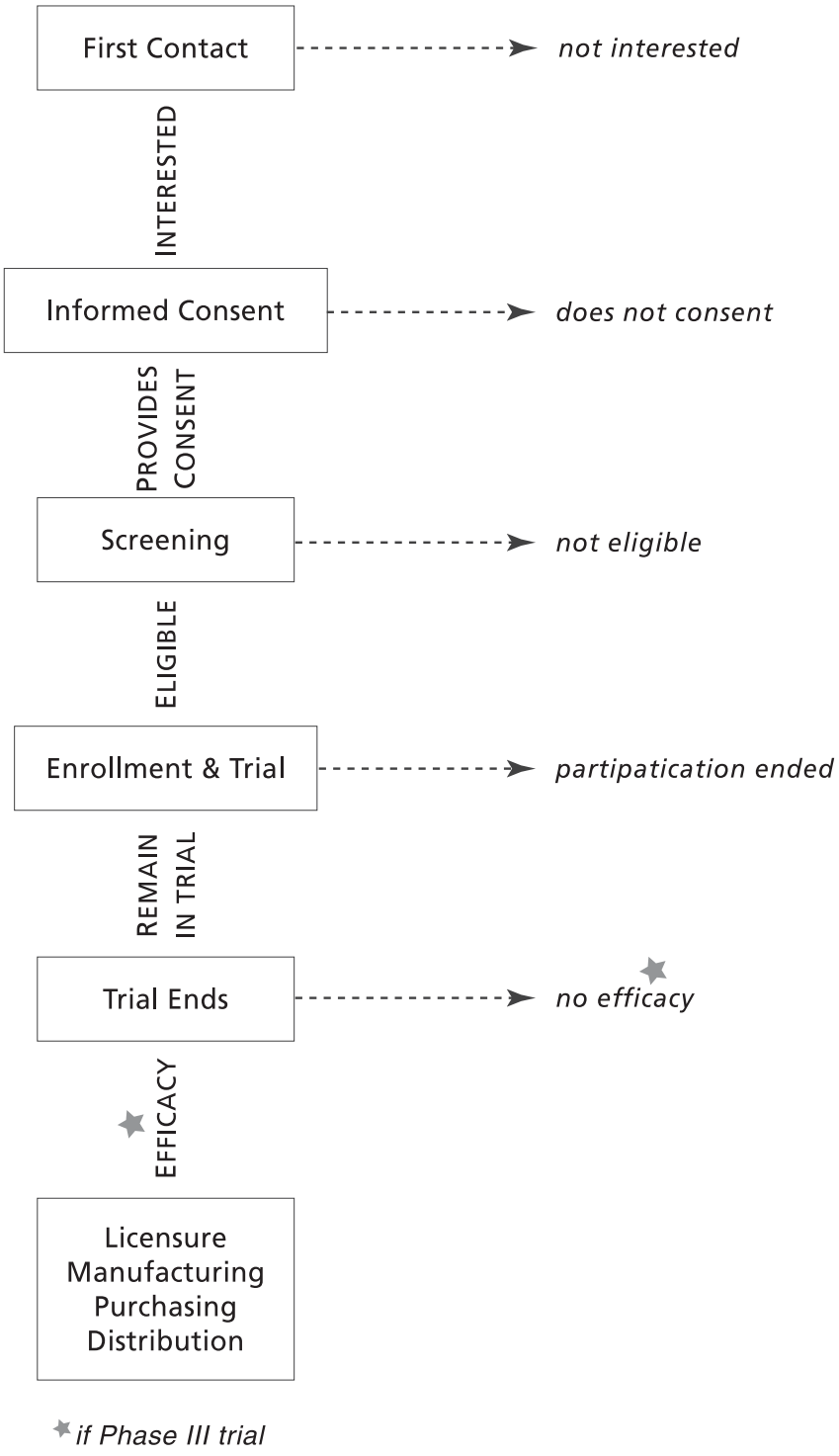
For the purpose of this guide, HIV vaccine trial participation is broken down into 6 easily recognizable stages, from the point of view of trial volunteers. These stages serve as the framework to introduce various ethical issues related to HIV vaccine research and development.

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 must decide 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	Enrollment & The Trial	The stage when the HIV vaccine research activities are conducted.
Stage 5	Trial End & 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.

It is important to remember that trial participation, as outlined here, is a general model that may vary depending on the phase of clinical research (I, II, IIB, or III), the specific trial site, trial sponsor, and/or the country where the trial is taking place. This outline provides a basic description of the process and a starting point for community discussions about the ethical considerations of HIV vaccine research.

This is flow chart depicts what trial volunteers will experience during the course of a trial.



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 can happen in many ways, such as through a community meeting, an advertisement in a newspaper, a flier or brochure posted in the community, or through someone you know. 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. If so, you should ask for basic information about HIV and 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.

Some of the information they are likely to provide:

- the purpose of the trial, i.e. to test an experimental HIV vaccine
- a brief list of the required characteristics of trial volunteers, like being HIV negative, healthy, at low or high risk of HIV infection, etc.
- compensation or benefits, if any, offered as part of participating in the trial
- how long the trial will last
- information to contact someone else for more details

Things to Think About

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/AIDS? 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 your 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.

SOME THINGS YOU CAN DO:

Learn more about who is involved in the research

Who is conducting the research? Is it sponsored by the government, a private company or a nonprofit organization? Have they done any other research in your community? What kind of a reputation do they have in the community? Finding out more about who is conducting the research will give you an idea of what to expect and perhaps raise some important questions you will want to ask them.

Make a list of questions to bring with you

Part of being in a clinical trial is being able to make decisions based on available information. Before meeting with the research staff, prepare a list of questions about the trial to make sure you understand everything. Some sample questions:

- How long will the trial last?
- Who do you want in the trial?
- Are there any known risks I should be aware of?
- What are the benefits, if any?
- How much of my time will being in the trial take?
- What are my rights and responsibilities as a trial participant?
- Is there any reimbursement or compensation for my participation?
- What happens if I experience a research-related injury?
- Who do I contact if I have any questions or concerns about the research study?
- Has this experimental vaccine been tested in people previously?

Consult your local HIV/AIDS service provider or information resource

Ask them if they are familiar with the research project you are interested in. See if they know the research institute or the trial sponsor. They may be able to provide you with useful information either about the trial or about the group conducting the research. They should also be able to provide basic HIV/AIDS education when needed.

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.

NOTES:

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.

You will be given a lot of information about the HIV vaccine research and time to go over the information, ask questions and talk with family, friends, doctors, and others. Then you will be asked to decide if volunteering is right for you. Information about the clinical trial should be provided in a way and in languages that are easy for you to understand.

NOTES:

UNAIDS Guidance Point 12

INFORMED CONSENT

Independent and informed consent based on complete, accurate, and appropriately conveyed and understood information should be obtained from each individual while being screened for eligibility for participation in an HIV preventive vaccine trial, and before s/he is actually enrolled in the trial. Efforts should be taken to ensure throughout the trial that participants continue to understand and to participate freely as the trial progresses. Informed consent, with pre- and post-test counseling, should also be obtained for any testing for HIV status conducted before, during and after the research.

UNAIDS Guidance Point 13

INFORMED CONSENT - SPECIAL MEASURES

Special measures should be taken to protect persons who are, or may be, limited in their ability to provide informed consent due to their social or legal status.

UNAIDS Guidance Point 15

MONITORING INFORMED CONSENT AND INTERVENTIONS

A plan for monitoring the initial and continuing adequacy of the informed consent process and risk-reduction interventions, including counseling and access to prevention methods, should be agreed upon before the trial commences.

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

Things to Think About

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.

NOTES:

THE FIVE KEY COMPONENTS OF ANY INFORMED CONSENT:

1) Information

Have you been provided all relevant information about the research, the experimental vaccine being tested and any other products being tested? You must be provided all available information in order for the informed consent process to work.

2) Comprehension

Did you understand the information presented to you? Informed consent requires more than just getting information. It requires you to understand what is being asked of you, what risks you might be taking, what benefits, if any, there might be. Do you feel you comprehend what volunteering means?

3) Freedom

Do you have the freedom to decide if you want to volunteer? Some people do not have the legal freedom to make such a decision, for example minors. Still others may not have the social freedom to make such decisions, for example some cultures require permission from a family or community leader before making such decisions. Did you decide or did someone else decide for you?

4) Capacity

Do all the volunteers have the capacity to understand and agree to participate in the clinical trial? Some people have a limited capacity, such as those with mental illness.

5) Explicit consent

Did you explicitly agree to volunteer for the trial? This is often documented by having you sign an informed consent document.

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.

NOTES:

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.

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. Inclusion criteria are characteristics that a volunteer must possess in order to be enrolled in the trial.

Things to Think About

Vaccine Induced Sero-positivity

Experimental HIV vaccines that stimulate the production of antibodies may cause a person to test HIV 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 clinical 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.

Exclusion criteria are characteristics that will exclude a volunteer from enrollment. Examples of what may affect a volunteers' eligibility to participate in a clinical trial include:

- age
- medical history
- pregnancy, or plans for pregnancy
- ability to make follow-up appointments
- certain medications a volunteer is taking
- level of risk for HIV infection
- HIV status

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.

Things to Think About

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 volunteer 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 HIV infected? 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.

Finding out you are not eligible to volunteer for the clinical trial does not mean you cannot contribute to the HIV vaccine development effort. You may be eligible to volunteer for another study, and there are other ways to contribute to the search for a preventive HIV vaccine. See page 27.

NOTES:

STAGE 4: ENROLLMENT & 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. Research staff may even ask you to call them each day for a few days to report your health status.

Researchers should provide you with HIV test 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. This is a way of honoring the principle of beneficence.

UNAIDS Guidance Point 11

CONTROL GROUP

As long as there is no known effective HIV preventive vaccine, a placebo control arm should be considered ethically acceptable in a phase III HIV preventive vaccine trial. However, where it is ethically and scientifically acceptable, consideration should be given to the use in the control arm of a vaccine to prevent a relevant condition apart from HIV.

UNAIDS Guidance Point 14

RISK-REDUCTION INTERVENTIONS

Appropriate risk-reduction counseling and access to prevention methods should be provided to all vaccine trial participants, with new methods being added as they are discovered and validated.:

UNAIDS Guidance Point 15

MONITORING INFORMED CONSENT AND INTERVENTIONS:

A plan for monitoring the initial and continuing adequacy of the informed consent process and risk-reduction interventions, including counseling and access to prevention methods, should be agreed upon before the trial commences.

DOUBLE-BLIND & PLACEBO-CONTROL TRIALS

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. Individual volunteers will be assigned to a group at random and the groups will be similar to each other demographically. This means that there will be 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 vaccine and who is getting 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.

Ending participation early

Trial volunteers may end their participation before the trial is complete. This can happen for a variety of reasons. Following are examples of common reasons why a volunteer may end their participation in a trial early.

Side Effects

If you have a serious side effect during the trial, your participation may be ended. This is for your safety. If your body reacts negatively to the experimental vaccine you should not stay in the trial. You will be asked to come in for lab tests and may have more follow up testing. Your participation is still valuable and there is no reason for you to feel like you did not contribute to the research.

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. If data shows the vaccine works well, everyone in the trial should receive the vaccine, honoring the principle of beneficence.

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. It is important that you contact your trial counselor if you have to miss an appointment. Otherwise, too much time may pass between your visits and you may no longer be eligible to continue participating in the trial.

Becoming HIV Infected During the Trial

If you become infected with HIV during the course of the trial, you will no longer be eligible to participate. You should be provided information about where to go for services and what your options are. The trial sponsors may have committed to providing AIDS treatments to volunteers who become infected during the trial. You should find out if this is true for you and how you will be able to access appropriate care and treatment when you need it. 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. It could be because you learned something ne about the trial (through ongoing informed consent), or maybe volunteering is just too much for you right now. 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. Volunteering in any clinical trial is just that — volunteering and you can choose to stop at any time.

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Stage 5: Trial End & 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. Some people feel a real sense of loss at the end of a trial. The relationships you have made with the research staff may be very important to you. Losing the opportunity to regularly meet and share with them may be hard at first.

All trial participants should be provided with the trial results and be given an opportunity to ask questions about them. This is a way of honoring the principle of justice. However, it may take some time before you learn what the results of the trial are. There can be several reasons for this. Volunteers who were recruited very early in the trial will finish before those volunteers who joined the trial later. All volunteers must finish their final appointments before the data can be analyzed. Also, the trial may have been designed to follow volunteers who became infected with HIV during the trial, to see if the vaccine had an effect on disease progression. Additionally, compiling and analyzing data from a clinical trial takes a lot of time and effort.

You should be given some indication of when the researchers expect to announce their trial results. It is a good idea to make sure the staff has your correct contact information so you can be reached when the results are available. When the trial results are announced, you should also be able to find out if you received the placebo or the vaccine. This is the unblinding process. The results from the trial should be explained to you in a way that you understand. You should also have an opportunity to ask questions about the trial results.

Notes:

TRIAL RESULTS

Trying to understand the results from an HIV vaccine trial can be confusing. The results will be based on the initial trial end points (the questions the trial was designed to answer and that were stated in the protocol). The table below gives some examples of possible results from a clinical trial.

For Phase I	For Phase II	For Phase IIB	For Phase III
SAFE: There were no significant side effects or adverse reactions observed.	HIGH IMMUNOGENICITY: The vaccine stimulated significant immune response.	HINT OF EFFICACY: The vaccine seemed to reduce HIV infection, transmission, disease progression.	HIGH EFFICACY: The vaccine significantly reduced HIV infection, transmission, disease progression.
NOT SAFE: There were significant side effects or adverse reactions observed.	MEDUIM IMMUNOGENICITY: The vaccine stimulated moderate immune response.	NO HINT OF EFFICACY: The vaccine seemed not to reduce HIV infection, transmission, disease progression.	MODERATE EFFICACY: The vaccine moderately reduced HIV infection, transmission, disease progression,
	NO/LOW IMMUNOGENICITY: The vaccine stimulated low or no immune response.	INDETERMIATE: The trial could not accurately provide an indication of efficacy of the vaccine.	LOW EFFICACY: The vaccine did not significantly reduce HIV infection, transmission,disease progression.
			INDETERMINATE: The trial could not accurately determine the efficacy of the vaccine.

As explained earlier, the principles of beneficence and non-maleficence require HIV vaccine clinical trials to be scientifically sound, with potential benefits that outweigh any potential risks. Therefore results from previous trials must merit further study of the product. Being able to understand the results from previous trials will help to determine the justification of further study of any experimental vaccine.

Just because a trial shows a product is not efficacious, it does not mean that your participation in the research project 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.

STAYING INVOLVED

Just because the trial you volunteered for is finished, your contribution to the effort to develop preventive HIV vaccines doesn't need to end. There are a variety of ways to stay involved — see page 27 for some ideas.

NOTES:

STAGE 6: AFTER EFFICACY

The end is far from near even after a vaccine is proven to effectively reduce rates of HIV infection, transmission, or disease progression. 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. In the case of HIV, often those who need it most also happen to be those with the least resources available to them. There are several issues that must be addressed to ensure that an effective HIV vaccine has the greatest impact. But steps to address these issues cannot wait for the completion of a phase III trial. Many actions can be taken in advance to ensure that a proven, efficacious vaccine is made available to people who need it most as soon as possible after the trial ends.

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.

At first glance, it might seem unnecessary (or even wasteful) to start planning now for delivering a vaccine that doesn't yet exist. But the world's experience with licensed vaccines demonstrates the terrible consequences of failing to tackle access issues early. Developing countries still wait an average of 20 years after a vaccine is licensed in industrialized countries before it starts reaching their own populations.

Licensing

Before any vaccine becomes available to the public, the makers of the vaccine must apply for a license. National regulatory agencies like the US Food and Drug Administration 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. Ongoing communication with regulatory agencies is critical to ensuring licensing as soon as possible.

Things to Think About

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.

UNAIDS Guidance Point 2

VACCINE AVAILABILITY:

Any HIV preventive vaccine demonstrated to be safe and effective, as well as other knowledge and benefits resulting from HIV vaccine research, should be made available as soon as possible to all participants in the trials in which it was tested, as well as to other populations at high risk of HIV infection. Plans should be developed at the initial stages of HIV vaccine development to ensure such availability.

Manufacturing

Making sure there is enough manufacturing capacity to produce enough vaccine for the world will take time. Building the capacity to mass produce any effective vaccine should be planned well in advance of product licensing because getting manufacturing plants up and running can take years. It is important that delays from manufacturing are minimized.

Purchasing

Historically, it has taken much longer for vaccines for other diseases licensed in industrialized countries to become available in developing countries. This must not happen in the case of HIV vaccines and advanced planning is critical to purchase enough vaccine to effectively address the global pandemic. Policy makers and advocates have been working on developing novel ideas for purchasing schemes and government incentives, but much more effort 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. This is a way of honoring the principle of justice. Factors to be taken into consideration include burden of HIV-related diseases, participation in HIV vaccine development, and public health infrastructure. Distribution of effective HIV vaccines will be greatly improved if governments work to distribute currently available vaccines for other diseases now. The infrastructure established to deliver these other vaccines will provide the necessary infrastructure needed later to distribute HIV vaccines when they become available.

Ways to Be Involved in Developing Preventive HIV Vaccines

Volunteering in a vaccine trial is a great way to contribute to the effort, but there are many other ways to be involved. Developing safe, effective and useful HIV vaccines is an enormous global endeavor, and your help is needed.

Join a community advisory board (CAB)

Every research institution is required to have a **CAB** or some other comparable mechanism for community consultation. CABs make important contributions to the design and conduct of clinical trials. A CAB is a group composed of community members who provide input at every step of the research process. CABs ensure that community issues are addressed and partnerships between researchers and communities are fostered. You do not need any special skills to join and the CAB will help you learn more about HIV vaccines. For information about CABs near you, contact the nearest HIV vaccine clinical trials site.

Notes:

Become an HIV vaccine advocate

Write or call your government leaders and ask what they are doing to accelerate ethical research on HIV vaccines and to promote better global health. Contact AIDS and health organizations in your area and ask what they are doing on behalf of preventive HIV vaccine research and development.

Make HIV vaccines part of your mission

If you are a staff member or supporter of an HIV/AIDS organization, health advocacy group, or civic organization, make sure that HIV vaccines are part of your group's mission. Incorporate HIV vaccine issues into your group's advocacy agenda and education efforts.

Spread the word about HIV vaccines

Discuss HIV vaccines with people and help them understand the role vaccines can play in controlling HIV/AIDS. Use local meetings and networks as an opportunity to discuss HIV vaccine development and address people's questions and fears.

Learn more

Learn more about HIV vaccine research and development. Keep yourself updated about advances in the effort and share what you learn. The AIDS Vaccine Clearinghouse (www.aidsvaccineclearinghouse.org) is a good starting point for information.

NOTES:

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SECTION 3
More Resources

There are many excellent resources that provide additional information on related topics.

Ethics and human subject research	• Belmont Report • Declaration of Helsinki • International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use • International Ethical Guidelines for Biomedical Research Involving Human Subjects • Nuremburg Code
HIV vaccine research	• The AIDS Vaccine Clearinghouse • Ethical considerations in HIV preventive vaccine research, a UNAIDS Guidance Document • ICASO Primer: Developing Vaccines for HIV and AIDS: An Introduction for Community Groups • ICASO Primer: The Science of HIV/AIDS Vaccines: An Introduction for Community Groups
HIV vaccines as part of a comprehensive response to the pandemic	• AVAC Handbook, Second Edition • Getting the Global House in Order, AVAC Report • HIV-1 vaccine trials and tribulations in The Lancet, September 2003 • Provision of treatment in HIV-1 vaccine trials in developing countries in The Lancet, September 2003.

DOCUMENTS

AIDS Vaccine Clearinghouse Website
AIDS Vaccine Advocacy Coalition
• www.aidsvaccineclearinghouse.org/

AIDS Vaccine Handbook, Second Edition
AIDS Vaccine Advocacy Coalition, 2005
• www.avac.org/handbook

Belmont Report

On July 12, 1974, the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was formed and charged to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects. They also developed guidelines to ensure that such research is conducted in accordance with those principles.

- www.ohsr.od.nih.gov/guidelines/belmont.html

Declaration of Helsinki

Written by the World Medical Association, this declaration for the medical profession focuses on protecting research subjects. Its general principles are the underpinnings of all subsequent, more specific standards.

- www.ohsr.od.nih.gov/guidelines/helsinki.html

Ethical considerations in HIV preventive vaccine research

UNAIDS guidance document, May 2000

Eighteen guidelines were developed after meetings convened by the UNAIDS Secretariat to define the ethical concerns involved in HIV vaccine research. The meetings included lawyers, activists, social scientists, ethicists, vaccine scientists, and epidemiologists, representatives of NGOs, people living with HIV/AIDS, and people working in health policy.

- www.who.int/vaccine_research/diseases/hiv/en/JC072-EthicalCons-E.pdf

HIV-1 vaccine trials and tribulations

The Lancet September 2003

- www.thelancet.com/journal/vol362/iss9388/full/llan.362.9388.talking_points.27260.2

HIV Vaccine Glossary

- www.aidsvaccineclearinghouse.org/glossary.htm

ICASO Primer: Developing Vaccines for HIV and AIDS: An Introduction for Community Groups

- www.icaso.org/CommunityPrep_VaccinePrimer_WebVersion_EN.pdf

ICASO Primer: The Science of HIV/AIDS Vaccines: An Introduction for Community Groups

- www.icaso.org/VaccinesSciencePrimer_WebVersion_EN.pdf

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

- www.ich.org

International Ethical Guidelines for Research Involving Human Subjects

Council of International Organizations for Medical Sciences (CIOMS)

- www.cioms.ch

Nuremberg Code

This code of conduct was developed by an international tribunal after World War II to prevent abusive research. It specifies that only qualified researchers may conduct human research using appropriate research designs, with a potential benefit greater than the risks taken. It codified that informed consent is absolutely essential and that participants must be free to withdraw from the research at any time.

- www.ohsr.od.nih.gov/guidelines/nuremberg.html

Provision of treatment in HIV-1 vaccine trials in developing countries

The Lancet September 2003

- pdf.thelancet.com/pdfdownload?uid=llan.362.9388.health_and_human_rights.27206.1&x=x.pdf

Organizations

AAVP - The African AIDS Vaccine Programme
www.who.int/vaccine_research/diseases/hiv/aavp/en/

AVAC - AIDS Vaccine Advocacy Coalition
www.avac.org

AFAO - Australian Federation of AIDS Organizations
www.afao.org.au/index_afa_771.asp

Canadian HIV/AIDS Legal Network
www.aidslaw.ca

HAVEG - HIV/AIDS Vaccines Ethics Group
www.saavi.org.za/haveg.htm

HVTN - HIV Vaccine Trials Network
www.hvtn.org

IAVI - International AIDS Vaccine Initiative
www.iavi.org

ICASO - International Council of AIDS Service Organizations
www.icaso.org

KAVI - Kenyan AIDS Vaccine Initiative
www.kaviuon.org

SAAVI - South African AIDS Vaccine Initiative
www.saavi.org.za

UVRI - Ugandan Virus Research Institute
www.iavi.org/uganda

USMHRR - United States Military HIV Research Program
www.hivresearch.org/vaccine/research.html

VRC - Vaccine Research Center
www.niaid.nih.gov/vrc

WHO-UNAIDS HIV Vaccine Initiative
www.who.int/vaccine_research/diseases/hiv/en/

NOTES:

autonomy: see principle of autonomy.

beneficence: see principle of beneficence.

CAB (community advisory board): a committee composed of community members who provide input at every step of the research. CABs ensure that the concerns and issues of communities are addressed and that partnerships between research and communities are fostered.

clinical research: research that involves human beings.

coercion: the act of compelling by force of authority; in the case of HIV vaccine research this refers to compelling individuals to participate in HIV vaccine clinical trials.

control group: the group in a clinical trial that receives placebo.

data safety and monitoring board (DSMB): this board reviews data during a trial to ensure the safety of trial participants. If the board sees any indication that the vaccine is harming volunteers, they will have the research study stopped. If during an efficacy trial the vaccine is clearly effective, the study may be stopped and all volunteers will be provided with the vaccine.

double-blind: a trial design where neither the researchers nor the trial volunteers know who receives placebo and who receives the experimental vaccine until the close of the trial. See "unblinding".

efficacy: in vaccine research, the ability of a vaccine to produce a desired clinical effect, such as protection against a specific infection, at the optimal dosage and schedule in a given population. A vaccine may be tested for efficacy in phase III trials if it appears to be safe and shows some promise in smaller phase I and II trials.

ethics: the rules or standards governing the conduct of a person, a society or the members of a profession.

ethics review committee: a group composed of ethicists, researchers, community members and others who review plans and materials associated with human subject research to ensure that the principles of ethical human subject research are upheld.

immunogenicity: the ability of a vaccine to stimulate an immune response.

informed consent: an agreement signed by prospective participants in a clinical trial that indicates their understanding of: (1) why the research is being done; (2) what researchers want to accomplish; (3) what will be done during the trial and how long it will last; (4) what risks are involved; (5) what, if any, benefits can be expected from the trial; (6) what other interventions are available; and (7) the participant's right to leave the trial at any time.

IRB (institutional review board): a committee of physicians, statisticians, community advocates and others that reviews clinical trial protocols before they can be initiated. IRBs ensure that the trial is ethical and that the rights of participants are adequately protected.

justice: see principle of justice.

modulate disease: changing the natural course of disease; HIV vaccines that modulate disease would not prevent infection but would prevent HIV-related disease or reduce infectiousness.

non-maleficence: see principle of non-maleficence.

Phase I vaccine trial: a closely monitored clinical trial of a vaccine conducted in a small number of healthy volunteers. A phase I trial is designed to determine the vaccine's safety in humans, its metabolism and pharmacologic actions, and side effects associated with increasing doses.

Phase II vaccine trial: controlled clinical study of a vaccine to identify common short-term side effects and risks associated with the vaccine, and to collect information on its immunogenicity. Phase II trials enroll some volunteers who have the same characteristics as persons who would be enrolled in an efficacy (phase III) trial of a vaccine. Phase II trials enroll up to several hundred participants.

Phase III vaccine trial: large controlled study to determine the ability of a vaccine to produce a desired clinical effect on the risk of a given infection, disease, or other clinical condition at an optimally selected dose and schedule. These trials gather additional information about safety needed to evaluate the overall risk- benefit relationship of the vaccine and to provide adequate basis for licensing. Phase III trials usually include several hundred to several thousand volunteers.

placebo: an inactive substance administered to some study participants while others receive the agent under evaluation, to provide a basis for comparison of effects.

pre-clinical research: research that occurs in the laboratory, before testing in humans begins.

principles of ethical research: four principles to guide medical research involving human subjects, developed to ensure that research volunteers are treated with dignity and respect.

principle of respect for autonomy: researchers must not interfere with the potential trial participants' autonomy; research participants are allowed the freedom to make their own decisions and the freedom to perform the acts they decide on for themselves. This principle calls for special measures to be taken to protect those considered non-autonomous as a result of incapacity, and to protect those who may have reduced or threatened autonomy.

principle of non-maleficence: researchers must not act in ways that will harm or injure potential trial participants, or the communities they come from; researchers must strive to minimize the risks and inconveniences to trial participants.

principle of beneficence: researchers must act in ways that promote the welfare of the trial participants, or the communities they come from, and take active steps to maximize potential benefits, and to balance risks and costs against benefits.

principle of justice: social benefits and social burdens must be distributed equally between communities participating in clinical research and those communities sponsoring the research; also known as distributive justice.

social harm: the experience of social discrimination or hardship resulting from association with HIV vaccine research.

sterilizing immunity: an immune response that completely eliminates an infection.

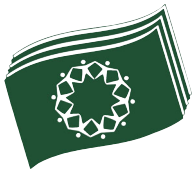
therapeutic HIV vaccine: a vaccine designed to boost the immune response to HIV in a person already infected with the virus; referred to as an immunotherapeutic vaccine.

unblinding: the act of revealing who received placebo and who received the experimental vaccine during a vaccine trial.

vaccine: a preparation that stimulates an immune response that can prevent infection or create resistance to infection.

vaccine induced sero-positivity: falsely testing HIV positive on standard ELISA tests, due to antibodies induced by a vaccine.

Notes:



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