

# Conduct of HIV Prevention Clinical Trials

## Introduction

The best way to determine the safety and efficacy (the ability to prevent infection or delay disease progression) of a new HIV prevention candidate, such as an HIV vaccine or microbicide, is by conducting human clinical trials. The testing process occurs through a series of clinical trials, in a range of populations and locations throughout the world, particularly areas with high HIV incidence.

## Pre-clinical testing

Before being tested in humans, an HIV vaccine or microbicide candidate product first undergoes pre-clinical testing in the laboratory and in animals to determine whether it shows promise as an intervention that is both safe and effective. For a candidate HIV vaccine or microbicide to advance through human clinical trials, pre-clinical data must suggest: (a) that the product is unlikely to harm people, and (b) that it may benefit people. If these conditions are met, the product can proceed into human clinical trials.

## Clinical trials

After an HIV vaccine or microbicide candidate shows promise in pre-clinical testing, it enters human clinical trials designed to test the product's safety profile in people and its ability (or 'efficacy') to prevent infection or delay disease progression. Clinical trials are the most reliable method of determining whether a new drug or treatment can be used safely in specific populations and whether it actually works.

## Phases of clinical trials

There are three standard 'phases' of human clinical trials that HIV vaccines and microbicides undergo: safety; expanded safety and efficacy.

- ▶ **Phase I** – These trials generally take several weeks and enrol a small group of volunteers (typically between 10 and 100) to evaluate a candidate's safety, determine a safe dosage range, identify side effects and measure the acceptability of the product to trial volunteers. These studies are also known as 'safety' trials.
- ▶ **Phase II (or Phase I/II)** – The candidate being tested is evaluated for a longer duration (generally 1 to 12 months) in a larger group of volunteers (typically between 100 and 1000) to further evaluate its safety, appropriate dosage range and acceptability. These studies are also referred to as 'expanded safety' trials.

(Phase I and II trials can also provide valuable information about rates of new HIV infection, and offer opportunities to develop research sites and build collaborative partnerships with local communities which are all critical for the successful conduct of Phase III trials.)

- ▶ **Phase III** – These trials evaluate the product efficacy (the ability to protect people from HIV infection). Large numbers of volunteers (typically thousands) are enrolled in efficacy trials of HIV prevention interventions. If a candidate product successfully shows both safety and efficacy upon completion of a Phase III trial, market authorisation from regulatory authorities can then be sought. These studies are also known as 'efficacy' trials.
- ▶ Sometimes **phase IV** trials are conducted after a product is already approved and on the market to find out more about the intervention's long-term benefits, risks and optimal use, or to test the product in different populations of people.

## Trial operations

Every trial has a slightly different design (or 'protocol') which maps out what will be done, by whom and why. Generally, trials are randomised, placebo-controlled and double-blinded.

- ▶ Randomised means that the volunteers are randomly assigned to groups (or 'arms').
- ▶ Placebo-controlled means that some of the volunteers receive a substance (a 'placebo') which is indistinguishable from the candidate product but does not contain active drug.
- ▶ Double-blinded means neither the volunteers nor the trial staff know whether the volunteers are receiving the experimental candidate or placebo.

Trial staff may include doctors, nurses, other healthcare professionals and often community educators and recruiters. Volunteers in HIV prevention trials include HIV-negative people, some of whom may be at risk for acquiring HIV. Not all people who volunteer for a clinical trial can be enrolled in a trial. There are a variety of reasons why some people are ineligible for participation including, for example, being HIV-positive, pregnant or breast-feeding, outside of a pre-established age range, or unable or unwilling to commit to regular clinical visits or other trial requirements.

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### TABLE

#### Phases of clinical trials

Phase	Number of volunteers	Volunteers use product for	Purpose
I	10s-100s	1-4 weeks	Safety, dosing and acceptability
II	100s-1,000s	1-12 months	Expanded safety, dosing and acceptability
III	1,000s-10,000s	1+ years	Efficacy

Trial volunteers are monitored closely throughout the trial to see if the product causes any problems or negative reactions. Every trial has a Data Safety Monitoring Board (DSMB) to regularly look at the data, review all safety findings, consider the potential for harm to the trial volunteers and make suggestions on the further conduct of the trial.

During the trial, volunteers in both arms receive extensive counselling about HIV and safer sex. Volunteers are reminded at enrolment and at all study visits that there is no knowing whether or not the candidate is effective, and are provided with condoms and regular screening and treatment for sexually transmitted infections. Some trials facilitate male circumcision for volunteers or their partners should it be requested. Volunteers have the right to leave a study at any time and for any reason without negative consequences for them.

#### Frequently asked questions

##### Q: Why are efficacy trials of HIV prevention interventions conducted in places with high HIV incidence?

**A:** An HIV vaccine or microbicide candidate must be tested by large numbers of people at high risk of HIV infection in order to determine whether the product actually works to prevent new infections. This means that the countries in which efficacy trials conducted need both:

- High incidence of HIV (many new infections per year).
- Stable populations so that volunteers can be followed up easily.

These conditions exist primarily in sub-Saharan Africa as well as in some communities in Southeast Asia, Europe and the Americas. Early stage trials may also take place in countries with lower incidence of HIV, including the UK. It is important that HIV vaccine and microbicide candidates be tested in the communities that need them most to ensure product acceptability and community support in advance of product introduction on the market.

##### Q: How are the human rights of volunteers protected in trials?

**A:** The study protocol must comply with international and national regulatory and ethical guidelines for the protection of volunteers and be based on sound scientific rationale. Before a trial can begin, both national regulatory agencies (NRAs) and national/local ethics committees (Institutional Review Boards or IRBs) must approve the trial protocol. NRAs usually focus on ensuring the only trials undertaken are those that are scientifically valid. IRBs are independent committees of clinical researchers, physicians, statisticians, community representatives and other experts that usually focus on ethical conduct of trials, social value for the community, standards of care, informed consent and trial communications in the community. An independent Data and Safety Monitoring Board (DSMB) may also review trial data periodically throughout the trial to ensure volunteer safety. DSMBs have the authority to suggest stopping a trial at any point if it looks as though the:

- Trial has already proven that the candidate product is highly effective.

- Candidate product may be causing harm.
- Trial can no longer answer the original questions it was designed to answer.

##### Q: What is 'informed consent'?

**A:** 'Informed consent' is the process through which a potential trial volunteer is given information about a study in order to help them decide whether or not to volunteer for that trial and by which a volunteer authorises participation. Informed consent is strictly regulated by international codes of conduct and supervised by local ethics committees and ensures all trial volunteers have a clear understanding of the trial and the potential risks and benefits of trial participation. Informed consent is also an ongoing process that requires periodic discussions with volunteers to ensure their continued understanding of the trial and their consent to be involved. Steps are taken to ensure that consent is genuinely informed including through the development of materials in local languages and involving the community prior to and during the trial.

## Get involved

**NAT (National AIDS Trust) is the lead UK partner of the International AIDS Vaccine Initiative and the International Partnership for Microbicides. If you would like further information about the development of HIV vaccines or microbicides, or want to get involved in helping ensure they become a reality, please contact: [policyandcampaigns@nat.org.uk](mailto:policyandcampaigns@nat.org.uk)**

**In addition, the organisations listed overleaf can provide up to date information about global, regional and national HIV vaccine and microbicide efforts.**

## Factsheet 7: Conduct of HIV prevention clinical trials

### **Q: Are HIV prevention trials unethical because they use a placebo?**

**A:** Most drug trials compare one group of volunteers who receive the experimental product to another group that does not. The goal is to determine whether the group that receives the new product fares better than the comparison group. There is no other scientifically valid way of testing drugs without a comparison.

In some trials, the experimental product is compared to the placebo, while in other trials it is compared to the standard drug or intervention already marketed for that purpose. Ethically, placebos may be used in trials if there is no other drug known already to work, as is the case with HIV vaccines and microbicides. HIV prevention trials provide all volunteers with condoms, risk reduction counselling and treatment for sexually transmitted infections, and some also facilitate male circumcision for volunteers or their partners should it be requested. Therefore, they compare standard prevention methods plus the experimental drug to standard prevention methods plus a placebo.

All volunteers in a trial, regardless of whether they are assigned to the experimental or placebo arm, receive state-of-the-art prevention interventions that already exist and have been approved for use. The HIV prevention field has rejected as unethical any trial that would compare an experimental product to a placebo without providing condoms or other existing prevention services.

### **Q: What happens to volunteers who become infected with HIV during the trial?**

**A:** Each organisation conducting a clinical trial has 'standards of care' guidelines. Standards of care refers to the services, rights and protections provided to clinical trial volunteers including commitments to provide all trial volunteers with ongoing risk reduction counselling, male and/or female condoms, treatment for sexually transmitted infections, treatment for those who become infected with HIV during the course of the trial, and treatment and compensation in the unlikely event of any physical harm.

Advocates have worked hard to ensure that volunteers who acquire HIV during the course of any HIV prevention trial are assured access to HIV care and treatment, including antiretroviral drugs when needed. Antiretroviral treatment is becoming increasingly available and accessible in many countries. Where they are unavailable or inaccessible, such care is arranged through partnership with local services, or the creation of a reserve fund to pay for treatment. Many trials also try to facilitate access to care for those who test HIV positive at screening.

### **Q: Does volunteering in a trial increase risk of HIV infection?**

**A:** Regrettably, in settings where HIV prevention trials are underway, the background rate of new HIV infections is high. Usually being in a trial does not increase risk of becoming HIV infected. In fact, many volunteers reduce their risk as a result of receiving trial-provided condoms and counselling.

Nonetheless, some trial volunteers will acquire HIV during the course of a trial because they are unable, despite assistance and counselling, to insist on consistent condom use with their partners. That risk is not a result of the trial but rather a reality of life for many volunteers in their community.

### **Q: How are communities involved in clinical research?**

**A:** Organisations conducting clinical trials are also using a variety of approaches to learn about community perspectives and engage community members as partners. Community outreach activities may include sponsoring education programs, holding periodic community forums, surveying community members, communicating with local and national media, creating 'community advocate' positions on trial staff and collaborating with non-governmental organisations to inform communities about the research and seek their input. Community Advisory Boards are committees composed of community members who provide input at various steps of the research process and ensure that the concerns and issues of communities are addressed and that partnerships between researchers and communities are fostered.

## Sources of information

### **NAT (National AIDS Trust)**

[www.nat.org.uk](http://www.nat.org.uk)

NAT is the UK's leading charity dedicated to transforming society's response to HIV.

### **International AIDS Vaccine Initiative**

[www.iavi.org](http://www.iavi.org)

Iavi is a non-profit product development partnership working to accelerate the development of a vaccine to prevent HIV infection and AIDS.

### **International Partnership for Microbicides**

[www.ipmglobal.org](http://www.ipmglobal.org)

IPM is a non-profit product development partnership established in 2002 to prevent HIV transmission by accelerating the development and availability of a safe and effective microbicide for use by women in developing countries.

### **AIDS Vaccine Advocacy Coalition**

[www.avac.org](http://www.avac.org)

AVAC is an international, non-profit organisation that uses education, policy analysis, advocacy and community mobilisation to accelerate the ethical development and eventual global delivery of HIV vaccines and other new prevention options as part of a comprehensive response to the pandemic.

### **Global Campaign for Microbicides**

[www.global-campaign.org](http://www.global-campaign.org)

GCM is a diverse network of advocates and non-governmental organisations working to expand HIV prevention options and encourage ethical research that involves civil society.