

Microbicide clinical trials:

How do they work?

What ethical guidelines must be followed?

Why do we need microbicides trials?

Every new drug, not just candidate microbicides, must go through series of tests before we can call them truly safe and effective. Before a country is to make a new drug available to its population, the drug regulatory board in that country must have information on how the drug affects human beings. This can only be made available if people are allowed to test the product. Testing of a microbicide candidate among people is therefore a necessary part of microbicides development.

Testing microbicide candidates in laboratories and in animals is called pre-clinical trials. Once that process is completed, the candidates that appear to be safe are moved into clinical trials, where they are tested among people. There are 3 stages or *phases* of clinical trials. Phases I and II focus primarily on examining whether the product is safe for people to use and what side-effects it may cause. Phase III trials, and sometimes an additional part of the second phase (known as Phase IIb), focus primarily on looking at whether the candidate microbicide works or not. Because of this, Phase III trials are also referred to as effectiveness trials.

The following table shows the usual number of participants,¹ length, and purpose of different phases of clinical trials. It is important to remember that a candidate microbicide is first tested with a very small number of volunteers in order to make sure that it is safe for human use. It cannot be tested among larger numbers of people until its safety has been established. Tests with more participants, however, need to occur in order to check whether the product works.

Trial Phase	Number of Participants	Participants Use Product For	Purpose
Phase I	20 to 100	1-2 weeks	Safety
Phase II	200 to 400	6-18 months	Safety
Phase IIb	200-800	6-12 months	Safety and effectiveness
Phase III	3,000 to 10,000	1-2 years	Effectiveness

How safe are the candidate microbicides that are tested among people?

Candidate microbicides are first tested in laboratories and with animals before these products move into tests with people. All these laboratory and animal tests look to see if the candidate microbicide might harm people. Testing is stopped immediately on any product appearing to be harmful.

Why do trials have to take place in developing countries among poor women?

A vaginal microbicide has to be tested by large numbers of women at high risk of sexually transmitted HIV in order to determine its effectiveness, so Phase III trials are conducted in communities with:

¹ Occasionally IIb trials are conducted with significantly greater numbers of participants. This is occurring with the VOICE study, for example, in which 4,200 women will be enrolled and followed for 14-35 months. Advanced trial phases (after safety has been demonstrated) are not always sharply separated in prevention trials since the data gathering data processes are very similar in Phase IIb and III prevention trials.

- High incidence of HIV (many new infections per year).
- A stable population (people who tend not to move from place to place) so that participants can be followed up easily.
- No injecting drug use or other sources of HIV risk among the participants.

These conditions exist mainly in sub-Saharan Africa and in some communities in India and Southeast Asia. Communities with high rates of HIV among women in North America and Europe also tend to have high rates of injecting drug use, which could confuse the trial results. If a woman in such a community becomes HIV positive, it is difficult to know for certain if she was exposed to HIV sexually or through shared drug use equipment.

How well-informed are the participants in the trials?

Volunteers give ‘informed consent’ at pre-screening, at screening, and again at enrolment once they are found to be eligible to participate in a trial. ‘Informed consent’ means that volunteers must understand exactly what is happening and make their own decisions about whether or not to participate in the trial. They undergo pre-screening (which will typically include preliminary questions and explanation of the trial) and screening (which will include an HIV test) before actually enrolling in the trial. These processes take place on different days in order to give volunteers time to think about what trial participation involves and give them time to change their minds, if necessary. Participants are also free to leave the study whenever they wish and for any reason at all. They are only required to return whatever study products they have received.

The World Health Organization (WHO) has issued guidelines² on how informed consent procedures in trials must be done. The governments of the countries hosting the trials are also responsible for regulating the conduct of clinical trials within their country. Many governments and research trial networks also have their own rules that they follow in addition to the WHO rules³.

How are the human rights of participants protected in trials?

Before a trial can proceed, national and/or local Ethical Review Boards must approve the trial protocol. These boards exist to ensure that the only trials undertaken are those that are both scientifically valid and ethically conducted. A Data and Safety Monitoring Board (DSMB) also monitors the results of each trial as they become available. DSMBs have the authority to stop a trial if it looks as though:

- The test product is definitely effective;
- The test product may be causing harm; or
- The trial can no longer answer the original questions it was designed to answer.

Many people are not aware of their HIV status when they volunteer to participate in a trial. Phase I and II trials enrol both HIV-positive and HIV-negative participants since products need to be safe for use by both populations. All trials participants must agree to receive an HIV test before they enrol in a trial so that researchers know which trial arm to enrol them in.

Phase IIb and III prevention trials enrol only HIV-negative participants. This is because a product’s effectiveness (if any) is measured by comparing the rate of sero-conversions among participants in the active arm (those using the candidate microbicide) with participants in the control arm (those

² This is in a document called “UNAIDS/WHO 2007 Ethical Considerations in Biomedical HIV Prevention Trials.” View it online at http://data.unaids.org/pub/Report/2007/jc1399_ethical_considerations_en.pdf

³ For one example of how the informed consent process works, see a video developed by the Population Council for its Carraguard microbicide trial at http://www.popcouncil.org/microbicides/micro_vignettes.asp

using a comparison gel). Trial sponsors are responsible for designing microbicide clinical trials to protect the confidentiality of all volunteers, including people who are not eligible to join Phase IIb and Phase III trials because they test HIV positive during the screening process. A briefing paper with more information on HIV positive women's involvement in microbicide trials is posted on the Global Campaign for Microbicides' website at www.global-campaign.org.

Are women intentionally exposed to HIV or encouraged to have unprotected sex during microbicides trials?

Women in microbicides trials are never intentionally exposed to HIV or encouraged to have unprotected sex. Rather, the women in trials are counselled to use condoms and other prevention methods every time they have sex, as well as the microbicides or the comparison gel. The study groups have to be very large and in areas where there is a high risk of acquiring HIV sexually specifically because ethical trials have to give women this level of prevention services.

Does participating in a trial increase women's risk of HIV?

Being in a trial, by itself, does not increase a woman's risk of becoming HIV infected. In fact, many volunteers are at lower risk of HIV as a result of receiving trial-provided condoms and condom counseling in their own language. Women enrolled in a Phase IIb or III microbicide trial usually have a lower overall rate of new HIV infections than their peers in the same community who are not part of the trial.

Even in trials with products that are completely safe, some trial participants acquire HIV during the course of the 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 women in their community.

As noted above, DSMBs also carefully monitor trials by examining the data collected at regular intervals while the trial is going on. They have the power to stop a trial if they think that there is any chance that candidate microbicide is placing women at risk. This happens very, very rarely but it did happen with a trial of a candidate microbicide called Cellulose Sulfate (CS). The trial was stopped in February 2007, as soon as the DSMB saw a slight signal of possible harm. For more information about the CS trial, please see <http://www.global-campaign.org/Cellulose-Sulfate.htm>.

How do researchers know if the product works if trial participants are using condoms and have access to other HIV prevention services during the trial?

If all trial participants were able to use condoms consistently, it would be impossible to evaluate a candidate microbicide's effectiveness. Even with the best prevention counseling and access to condoms, not all people can get their partners to use condoms every time. This is why we need microbicides. Microbicides trials measure whether use of the active product offers any protection among those who do not manage to use condoms 100% of the time during the trial.

What happens to women who become infected with HIV?

Advocates have worked hard to ensure that those who acquire HIV during the course of any HIV prevention trial have access to HIV care and treatment, including antiretroviral drugs when needed. The Global Campaign's 2005 *Consensus Statement on Standard of Care*⁴ called on all trial sponsors to establish durable mechanisms prior to the start of any trial to make sure that all participants who become HIV positive during the trial have on-going access to HIV treatment and care when they need it. International guidance from UNAIDS (2007) on this issue also says that researchers and sponsors must ensure access to comprehensive care for HIV infection, including access to antiretroviral therapy (ART) for trial participants who become HIV positive during a trial.

In 2008, the Global Campaign convened a meeting on 'Operationalising Access to HIV Treatment and Care', which focused on the challenges of ensuring life-long access to treatment and care for

⁴ See <http://www.global-campaign.org/ethics-resources.htm> for a copy of this document

HIV prevention trial participants who seroconvert during the trial. As a direct result of that meeting, the Campaign has formed a small working group of researchers, policy-makers, and community advocates to help the HIV prevention field move forward on this issue.

Aren't clinical trials sponsored by large pharmaceutical companies that want to test their products on the poor and sell them to the rich?

Some of the new candidates being tested were developed by large pharmaceutical companies. But, to date, none of the microbicide trials or trials of other new HIV prevention tools (NPTs) have been sponsored by these companies. Most NPT trials are sponsored by public health-focused non-profit groups or academic institutions. Some smaller pharmaceutical companies are involved in the development of microbicides and have partnered with these non-profit groups or academic institutions to test their products.

The reason that large pharmaceutical companies are not involved in the research of microbicides is that the profit for them appears too low. The primary consumers of the vaginal microbicides currently being developed are likely to be poor women in developing countries. Since these women have very limited economic power, the microbicides (once proven safe and effective) will likely be provided at cost with public health and development funding. The lack of profit motive inherent in this kind of product distribution discourages investment by large pharmaceutical products.

What is the Global Campaign's role in clinical trials?

The Global Campaign for Microbicides is committed to ensuring that, as the science proceeds, the rights and interests of trial participants, users and communities are fully represented and respected. As NPT trials roll out, the Global Campaign is specifically working to:

- Assure that trial communities and civil society have a voice in trial design and ethics issues.
- Forge consensus around ethical debates (such as access to care for trial participants who seroconvert) that could delay progress.
- Negotiate the difficult line between urgency of the HIV epidemic and maintaining rigorous ethical standards.
- Build capacity in activist/community sectors for ethical deliberation and debate.

The Campaign offers resources, assistance, and support to advocates and communities working to become active, well-informed and respected participants in these deliberations.

For more information:

For more information about the Global Campaign's work in this area, please go to our Ethics and Community page, http://www.global-campaign.org/ethics_community.htm.

On our web page, you can also download our latest reports and fact sheets on ethics and community involvement including:

“Rethinking the ethical roadmap for clinical testing of microbicides: Report on an International Consultation” was published by the Global Campaign for Microbicides, May 2005. It is available on line at <http://www.global-campaign.org/researchethics.htm>.

This and other fact sheets can all be downloaded at www.global-campaign.org/download.htm.

The Global Campaign for Microbicides (GCM) is a civil society organization working to ensure the ethical and accelerated development of, and widespread access to, new and existing HIV-prevention options—especially for women. Visit our website: www.global-campaign.org or email: info@global-campaign.org