



Microbicide clinical trials: Are they ethical?

In clinical trials, human participants test candidate microbicides to determine whether they are (a) safe and (b) effective. Randomised clinical trials are the most reliable method of determining whether a new drug or treatment can be used safely by a large cross-section of the population and whether it actually works. One of the concerns frequently expressed in connection with such trials, however, is that poor people, especially those in developing countries, may be used as 'guinea-pigs' in the research process and their rights as trial participants may not be adequately protected.

This fact sheet provides a brief explanation of how microbicide trials are conducted and outlines what microbicide advocates are doing to ensure that the highest ethical standards are maintained throughout the process of testing candidate microbicides.

How are microbicides tested?

Any new product is thoroughly researched and tested in the laboratory and in animals before it is tested on people. To get approval for human testing, a researcher must first show data demonstrating: (a) that the product is unlikely to harm people and (b) that it may benefit people. If both these conditions are met, the product is approved for human testing.

The first stage of testing a product in human beings is called a Phase I trial. In Phase I trials, the candidate product is used by 20-40 healthy volunteers for a limited period of time. These participants are monitored closely to see if the product causes any problems or negative reactions. Generally, several Phase I trials are conducted in increasingly diverse groups of participants. For example, the candidate microbicide may first be tested in healthy, HIV negative women. If those volunteers do not experience any negative reactions to the product, then it is tested among women in other settings and among those who may have other health problems (e.g. in developing countries and/or among women who are HIV positive). Sometimes, a separate Phase II study is conducted to examine safety among more women for a longer period of time.

If any evidence of potential harm emerges at any point, research on that candidate product is stopped and either the drug is changed in some way to make it safer or it is dropped from consideration as a potential microbicide. If the data generated from the safety trials do not produce any evidence of potential harm, then the candidate can go into an effectiveness trial, known as Phase III, to find out if it really works. Phase III trials involve a significantly greater number of participants than safety trials, ranging from 3,000 to 10,000 women.

It is important to remember that positive results in Phase I and II clinical trials do not mean that the product has been determined to be completely safe. These early Phases involve a relatively small number of volunteers. Completion of them simply means that the product appears to be safe thus far and that it is reasonable to move forward to a Phase III trial to gather additional information about product safety as well as efficacy.

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	Expanded safety, dosing, and acceptability
Phase III	3,000 to 10,000	1-2 years	Effectiveness

How do you know if a microbicide is effective?

A very large number of women (several thousand) have to be enrolled and followed over time in a Phase III trial to determine whether the microbicide helps reduce risk of acquiring HIV. The Phase III trial works by comparing two groups: (a) those receiving the best-known HIV prevention package plus the experimental microbicide gel and (b) those receiving the best-known prevention package plus the comparator gel. The comparator gel looks just like the product being studied but does not contain the active ingredient.

Researchers randomly assign women to be in one of two trial groups—known as “arms” of the study. Randomisation ensures that women in each group are similar in every respect except the matter under study – in this case, use of a test gel versus use of a comparator gel. Women are never deliberately exposed to HIV to see if the microbicide protects them.

Instead, researchers follow the two groups over time to see if the rate of new HIV infections is lower among those who received the candidate microbicide versus those who do not. If it is, this difference is the measure of the microbicide’s effectiveness.

Microbicide Clinical Trial Prevention Package

In microbicide trials all women are provided the best known prevention package. This consists of:

- Intensive condom and safer sex counselling
- Large supplies of free, high quality condoms
- Regular screening and treatment for curable STIs

Women are encouraged to use condoms, whether they are given the active microbicide or not.

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

Regrettably, in the settings where microbicide trials are underway, the background rate of new HIV infections is incredibly high. Usually being in a trial does not increase a woman’s risk of becoming HIV infected. In fact, many volunteers reduce their risk as a result of receiving trial-provided condoms and condom counselling in their own language. Frequently, women enrolled in a Phase III microbicide trial have a lower overall rate of new HIV infections than their peers in the same community who are not part of the trial.

Nonetheless, some trial participants will 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.

Very rarely the candidate microbicide itself may cause problems that could increase a woman’s risk of HIV infection. This is what happened with Cellulose Sulfate (CS) and why the Phase III CS trials were halted prematurely in February 2007. Once in a great while a product does not show any evidence of increasing risk until it is in a Phase III trial and being used by several thousand women.

Before the Phase III trials of CS started, scientists had scrutinised the data from eleven separate safety trials that had been conducted to see if CS was safe. These studies were conducted in Africa, India, the US and Europe. None of them produced any data suggesting that the product could cause harm. In particular, there was no evidence of vaginal lesions (as occurred with the Nonoxynol-9 trial stopped in 2000). CS acts in different way against HIV than N-9 and seemed to have a good safety profile.

For more background on the decision to stop the cellulose sulphate trial go to: <http://www.global-campaign.org/Cellulose-Sulfate.htm>.

How do researchers know if the product works if women are using condoms during the trial?

If all trial participants were able to use condoms consistently, it would indeed be impossible to evaluate microbicide effectiveness. The very reason we need microbicides, however, is that even with state of the art prevention counselling and access to condoms, not all women can get their partners to use condoms every time. Microbicides trials measure whether use of the active product offers any protection among those women who do not manage to use condoms 100% of the time during the trial.

Why do Phase III trials have to take place in developing countries?

A microbicide has to be tested by large numbers of women at high risk of sexually transmitted HIV in order to determine its effectiveness. This means that the countries in which Phase III trials are conducted must have:

- High incidence of HIV (many new infections per year)
- Stable populations so that participants can be followed up easily
- Virtually no injecting drug use or other sources of HIV risk among women

These conditions exist in parts of sub-Saharan Africa and in some communities in India and Southeast Asia. Communities where HIV incidence is high among women in the North America and Europe also tend to have high rates of injecting drug use, which could confuse the trial results by introducing other sources of exposure to HIV. Also it is important the microbicides be tested in the communities that need them most.

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 vary across the world, but 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) oversees the trial to monitor results in real time, as they become available. This DSMB has the authority to stop a trial if it looks as though:

1. the test product is definitely effective
2. the test product may be causing harm
3. the trial can no longer answer the original questions it was designed to answer

Many of the women volunteering to participate in trials are not aware of their HIV status. Phase I and II trials enrol both HIV-positive and HIV-negative participants since products need to be safe for use by both populations. Phase III trials; however, seek to enrol only HIV-negative participants because the rate of sero-conversion among trial participants is the trial's primary end point (its way of measuring effect).

It is vitally important that sponsors design microbicide clinical trials to protect the confidentiality of all participants and potential participants, including those HIV-positive individuals who are excluded from trial participation. For a more detailed discussion of the issues related to positive women, please refer to our fact sheet on HIV positive women and microbicides, **Factsheet #7**.

What happens to women who become infected with HIV?

Advocates have worked hard to ensure that women who acquire HIV during the course of any HIV prevention trial are assured access to HIV care and treatment, including antiretroviral drugs when needed. The Global Campaign's *Consensus Statement on Standard of Care* has called on all trial sponsors to establish durable mechanisms, prior to the start of a trial, to ensure women access to HIV care. Generally such care is arranged through partnership with local entities, or the creation of a reserve fund to pay for treatment. Many trials also try to facilitate access to care for women who test HIV positive at screening, by providing CD4 tests and other assessments that can help them qualify for locally available treatment programs.

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

One of the Global Campaign for Microbicides' core goals is to ensure that as the science proceeds, the rights and interests of trial participants, users and communities are fully represented and respected. As microbicide trials roll out, the Global Campaign is committed to:

- Giving voice to community and civil society perspectives on trial design and ethics issues
- Forging consensus around ethical debates that could delay progress
- Negotiating the difficult line between urgency of the HIV epidemic and maintaining rigorous ethical standards
- Building capacity in activist/community sectors for ethical deliberation and debate

The Global Campaign believes that ethics is a process of moral reflection, not a set of rules. Whose voice is part of the process is critically important to the 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 on ethics and community involvement:

"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>.

"Mobilization for Community Involvement in Microbicides Trials: Report from a Dialogue in Southern Africa" at <http://www.global-campaign.org/clientfiles/SA-community-involvement.pdf>. This report describes a framework for developing community involvement plans that are grounded in principles of partnership, mobilisation and sustainability, to help communities and research institutions to work together to implement scientifically rigorous and ethically sound clinical trials.

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