Fact Sheet #5

Clinical trials: Are they ethical?

In clinical trials, human participants test candidate microbicides to determine whether they are (a) safe and (b) effective. Randomized 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 done 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 drug is thoroughly researched 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: (1) that it is unlikely to harm people and (2) it may benefit people. If both these conditions are met, the test product is approved for human testing. In Phase 1 safety trials, the candidate product is used by a small number of volunteer participants for a limited period of time. These participants are monitored very closely to see if the product causes irritation or other adverse reactions. If it appears to be safe in a Phase 1 trial, it is tested by a larger number of volunteers in a Phase 2 safety trial. Phase 1 and Phase 2 microbicide trials enrol women in both industrialized and developing countries to find out if the test product can be used safely and without problems by most people.

- If safety is not demonstrated, research on that candidate is stopped and it is dropped from consideration as a potential microbicide.
- If safety is demonstrated, the candidate can then go into an effectiveness trial -- known as Phase 3 -- to find out if it really works. For reasons explained below, these Phase 3 trials have to be conducted in countries with high incidence of sexually transmitted HIV.

<table>
<thead>
<tr>
<th># of Participants</th>
<th>Participants use product for</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>20 to 100</td>
<td>1-2 weeks</td>
</tr>
<tr>
<td>Phase 2</td>
<td>200 to 400</td>
<td>6-18 months</td>
</tr>
<tr>
<td>Phase 3</td>
<td>3,000 to 10,000</td>
<td>1-2 years</td>
</tr>
</tbody>
</table>

How do you know if a microbicide is effective?

The Phase 3, or effectiveness, trial works by comparing two groups -- the best known prevention package plus the candidate microbicide and those receiving the best known prevention package plus the comparator gel. The comparator gel looks just like the drug being studied but does not contain the active ingredient.

Women are randomly assigned to one of the two arms of the trial. Randomization ensures that as a group, women in each arm are similar in every respect except the matter under study -- in this case, use of a test product versus use of a comparator gel. Women are never deliberately exposed to HIV to see if the microbicide protects them. Instead, researchers compare the two groups to see if the rate of seroconversion was lower among those who received the candidate microbicide versus those who do not. If it was, that difference is the measure of the microbicide’s effectiveness.
All trial participants receive the best known prevention package – which consists of intensive condom counseling, large supplies of free, high quality condoms and regular screening, and treatment if needed, for sexually transmitted diseases (STD). The women are encouraged to use condoms, whether they are given the active microbicide or not. A very large number of women (several thousand) have to be enrolled in the trial, in order to determine whether a reduced HIV infection rate (if one occurs) came about as a result of the microbicide, or because of condom use and other factors such as behaviour change or prompt treatment of STDs.

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

No. Participants do not increase their risk of becoming HIV infected as a result of being in the trial. In fact, many reduce their risk as a result of receiving trial-provided condoms and condom counselling in their own language. However, some women will nonetheless become infected during the trial because they are unable, despite assistance and counselling, to insist on consistent condom use with their partners.

Women in both arms of a Phase 3 trial generally have fewer HIV sero-conversions than women in the general community because of the risk reduction efforts described above (e.g. free condoms, condom counselling and STI screening and treatment). Every effort is made to ensure that women understand that they should not count on the test product to protect them from infection (since its effectiveness is unknown) and that using condoms is the best way to protect themselves. If participants cannot insist on condom use with their partners, however, their HIV risk may continue despite their trial participation. That risk is not a result of the trial but rather a reality of life for millions of women.

**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 3 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 3 trials are carried out must have:

- High incidence of HIV
- Stable population so that participants can be followed up easily
- Virtually no injecting drug use or other sources of HIV risk among women

These conditions are found across sub-Saharan Africa and in India and parts of Southeast Asia. Places where HIV is prevalent 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 HIV risk.

Large-scale microbicide trials can bring increased health care infrastructure, HIV prevention services and treatment access into highly impacted and resource-poor communities. How these services are provided and the extent to which they are continued after the trial is over is often the subject of intense ethical debate and scrutiny.

One of the Global Campaign’s functions is to help community members in trial areas become well informed about how clinical trials work. We also help research institutions understand the value of developing authentic partnerships with the communities in which trials are conducted. Building this capacity for sustainable collaboration both

- benefits the institutions seeking to do high quality ethical research and
• advances the efforts of community members who want research done locally to also facilitate longer-term improvements in their communities.

**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. Once the trial commences, 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 the test product is definitely effective, or definitely ineffective. The “best case” scenario would be for a microbicide’s effectiveness to be so readily apparent from early data that the trial could be discontinued and the product could be made publicly available to all who need it. This, however, has not yet occurred.

Many of the women volunteering to participate in trials are not aware of their HIV status. Phase 1 and 2 trials enrol both HIV positive and HIV negative participants since products need to be safe for use by both populations. Phase 3 trials, however, tend to enrol only HIV negative participants because the rate of seroconversion among trial participants is the trial’s primary end point.

Potential participants must agree to HIV testing to be considered for trial enrolment and those who test positive are generally not enrolled in Phase 3 trials (although some Phase 3’s are discussing involving HIV positive women in sub-studies). Women can be excluded from trial enrolment for a wide variety of reasons, however, including other health problems, pregnancy, or unwillingness to adhere to the trial protocol. In many communities around the world, people who are perceived to be positive face stigma and discrimination. For this reason, researchers and community groups must make it very clear that exclusion from the trial does not automatically mean that a woman is HIV-positive.

It is vitally important that microbicide clinical trials be designed 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?**

The package of HIV prevention and treatment provided during the trial is referred to as the ‘standard of care’. Intense debates occur over how the appropriate standard of care in international trials should be defined. Within the microbicides field, there is a strong commitment to improving the local standard of care, including HIV care.

Women who become HIV positive during microbicides trials are offered some level of access to Anti-Retroviral treatment (ART), depending on the trial. The drop in ART drug prices has made it more feasible to ensure treatment for women who sero-convert during the trial. As the local provision of ART expands, trial sponsors are actively reviewing their policies for treatment provision with host communities. Standard of care is one of the issues negotiated before the trial begins and communicated to volunteers considering enrolment. It is one of the factors potential participants weigh when thinking about what enrolling in the trial would mean for them. The grim reality in the developing world is that the standard of care available to trial participants is generally higher than that accessible to everyone else in the community.

**What went wrong with Nonoxynol-9?**

Women have used Nonoxynol-9 (N-9), a spermicidal compound, in birth control products since the 1950s. In the 1960s, governments began to require much higher levels of safety testing for new products. Because N-9 was already on the market, it was not required to undergo the rigorous testing that new products have to go through now.
Scientists started testing N-9 as a potential microbicide in the 1980s. The results of these trials varied widely, however, depending on the dosage and formulation of the N-9 product being tested and the participants’ usage patterns. Data from these studies were difficult to compare but, in general, infrequent use (once daily or less) or use of low dose products appeared to be relatively safe. Given the urgent need for a microbicide and the efficiency with which N-9 kills HIV, the research on N-9 continued until 2000. In July 2000, study data were released showing that even a low dose N-9 gel, if used with high frequency, could cause sufficient irritation to increase a woman’s risk of HIV infection.

At that point, research on N-9 as a candidate microbicide stopped completely. N-9 products are still on the market as contraceptives but are only recommended for vaginal use by women who are at low or no risk of HIV infection. Studies have also demonstrated that N-9 is significantly damaging to rectal tissue. In light of these findings, the Global Campaign for Microbicides has advocated (with some success) for the removal of N-9 from condoms. For more information on N-9, please see our Factsheet #9.

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. The process by which ethical decisions are developed, therefore, is very important. Whose voice is represented in the debate is as important as the subject of the debate. The Campaign offers resources, assistance and support to advocates and communities working to become active, well informed and respected participants in these debates.

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


Finally, this and other fact sheets can all be downloaded at [www.global-campaign.org/download.htm](http://www.global-campaign.org/download.htm).

The Global Campaign for Microbicides is a broad based, international coalition of organizations working to accelerate access to new HIV prevention options.

To find out more and get involved, visit our website: [www.global-campaign.org](http://www.global-campaign.org) or contact us:

c/o PATH, 1800 K Street NW, Suite 800, Washington, DC 20006 USA
Phone: +1 (202) 822-0033 Fax: +1 (202) 457-1466 Email: info@global-campaign.org
or
Rebekah Webb, 7th Floor, 98 rue du Trone, Brussels 1050, Belgium
Phone: +32 (0)2 507 1221 Fax: +32 (0)2 507 1222 Email: rwebb@global-campaign.org