Rethinking the Ethical Roadmap for Clinical Testing of Microbicides:

Report on an International Consultation

Prepared by the Global Campaign for Microbicides

Global Campaign FOR Microbicides

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Microbicide Basics

What is a microbicide?

The word microbicide (mi-KRO'-bi-sid) refers to a range of products that share a common characteristic: the ability to prevent the sexual transmission of HIV and other STD pathogens when applied topically in the vagina or rectum. These products do not yet exist, but they are now being developed and tested with large human populations in clinical trials. Future microbicides could be produced in many forms-gels, creams, suppositories, films, or in sponges or vaginal rings that slowly release the active ingredient.

When will microbicides be available?

To create a safe, effective product, scientists are now pursuing more than two dozen product leads. So far, 16 have proven safe and effective in animals and are being tested in people. With sufficient investment in the field, a successful microbicide could be on the market by the end of the decade.

Would a microbicide eliminate the need for condoms?

No. When used consistently and correctly, male or female condoms are likely to provide better protection against HIV and STDs than microbicides. But for those who cannot or will not use condoms-and in particular, for women whose partners refuse to use condoms-microbicides will save lives and could have a substantial impact on the HIV epidemic. A mathematical model projects that if even a small proportion of women in low-income countries used a 60 percent efficacious microbicide in half the sexual encounters where condoms are not used, 2.5 million HIV infections could be averted over 3 years.

Who is working on microbicide research and development?

To date, virtually all microbicide research has been conducted by nonprofit institutions, universities, and small biotech companies. The work has been primarily funded by charitable foundations and government grants. Public funds have contributed to microbicide development through support for basic science research, social and behavioral research, and support for clinical trial infrastructure. Large pharmaceutical companies have not significantly invested in microbicide development. As a classic "public health good," microbicides might yield tremendous benefits to society, but the profit incentive is low for private investment.

(*continued on inside back cover*)

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The Basics of Microbicides, continued from front inside cover

How does a microbicide work?

There are four basic mechanisms of action by which various candidate microbicides may work: (1) Killing or inactivating pathogens-some microbicides work by breaking down the surface or envelope of the virus or pathogen; (2) Strengthening the body's normal defenses-the body has several naturally occurring defense mechanisms that a microbicide may be able to supplement or enhance. Lactobacillus, for example, is a naturally occurring, "good" bacteria that helps protect the vagina by maintaining its acidic environment. This natural acidity helps foster an inhospitable environment for many pathogens, including HIV. Thus, the idea of developing a microbicide that supports the lactobacilli in performing this function is one potential mechanism of action being explored; (3) Inhibiting viral entry-some microbicides bind to viruses and bacteria to prevent them from binding to and infecting healthy cells. (4) Inhibiting viral replication-some candidates are being developed from the anti-retroviral drugs that HIV positive people use to lower the amount of virus in their bodies. Formulated as gels or creams, these drugs may be able to suppress replication of any HIV that enters the vagina or rectum during sex. If so, they could substantially lower the odds that the microbicide user will become infected.

Eventually, microbicide products will probably combine several of these mechanisms of action.

How are microbicides tested?

Any new drug is thoroughly researched in the laboratory and in animals before it is tested on people. In clinical trials, human participants test candidate microbicides to determine first, whether they are safe and, second, whether they are effective. In Phase 1 safety trials, the candidate product is used by a small number of volunteer participants for a limited period of time, with close monitoring to see if the product causes irritation or other adverse reactions. If it appears to be safe, it is tested by a larger number of volunteers in a Phase 2 safety trial. Phase 1 and Phase 2 microbicide trials enroll women in both industrialized and developing countries. The Phase 3, or effectiveness trial compares two groups-those who receive the microbicide plus condoms and those who receive a placebo plus condoms. The placebo looks just like the drug being studied but does not contain the active ingredient.

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

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 counseling in their own language. Some women will nonetheless become infected during the trial because-despite assistance and counseling-they are unable to insist on consistent condom use with their partners. Women in both arms of a Phase 3 trial generally have fewer HIV seroconversions than women in the general community because of the risk reduction efforts offered as part of the trial. Every effort is made to ensure that women understand that they should not count on the test product to protect them from infection-because its effectiveness is unknown-and that using condoms is the best way to protect themselves.

What is the Global Campaign for Microbicides, and what is its role in clinical trials?

The Global Campaign for Microbicides is a broad-based international movement of advocates working to expand access to new and existing user-controlled methods of HIV prevention. The Global Campaign is endorsed by 200 NGOs worldwide, 55 of whom serve as active Campaign partners. One of the Global Campaign's 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. It is committed to negotiating the difficult line between urgency of the HIV epidemic and maintaining rigorous ethical standards in the development of microbicide products. The Campaign offers resources, assistance, and support to advocates and communities working to become active, well informed participants in this process. Fact sheets, documents, and newsletters can be downloaded at www.global-campaign.org/download.htm.


Global Campaign
FOR Microbicides

1. Introduction: Rethinking the Ethical Roadmap

The shifting frontier of the microbicide challenge

Scientific and political challenges have dominated the field of microbicide development for the past decade—unlocking the secrets of the virus, identifying promising microbicide candidates, and mobilizing financial resources and political will. Our task has been to bring to reality a novel approach to HIV prevention that most of the scientific community viewed as wishful thinking just a few short years ago.

Remarkable progress has been made on both scientific and political fronts in recent years. From a "field" lacking even a name—much less significant research funding or a political constituency—the notion of a women-controlled method for HIV prevention has evolved into a global movement uniting researchers, foundations, governments, and thousands of women's health and AIDS activists. From virtually *no* funded research as of 1992, global investment rose from roughly $28 million in 1998 to nearly $140 million in 2004.[1] Scores of research papers are now being published annually, with results reported upon instantly through scientific meetings, AIDS conferences, and web media of hundreds of activist organizations.

Although the pharmaceutical industry still remains largely a bystander, a growing number of foundations and government agencies have joined the race for a low-cost, universally accessible microbicide. The United States Congress has introduced the Microbicides Development Act of 2005 to authorize increased federal funding for microbicide research and development and to mandate a clearly defined organizational unit at the National Institutes of Health (NIH) to spearhead this effort. Influential political figures, such as UK Prime Minister Tony Blair, have urged the G8 nations to focus on microbicides while continuing the race to develop vaccines and better treatments. And an eminent group of world scientists have pronounced microbicides one of the "top 10 most promising biotechnologies for improving global health.[2] "

While scientific and political challenges have guided our efforts over the past decade, the challenges and cutting edge of the next decade may be considerably different. Partly as a result of the field's successes, the frontier of microbicide development is taking on a new character. The determinative challenges that we face today may well be

[1] HIV Vaccines and Microbicides Resource Tracking Working Group. Public and philanthropic investments in preventive HIV vaccines and microbicides: 2000 to 2004: Preliminary report. New York: IAVI, AVAC, UNAIDS and the AMD. Available at: http://www.iavi.org/file.cfm?fid=9862.

[2] Daar AS, Thorsteinsdottir H, Martin DK, Smith AC, Nast S, Singer PA. Top ten biotechnologies for improving health in developing countries. *Nature Genetics*. 2002. 32(2): 229–232.

ethical, not scientific or political. And how thoughtfully and how well we respond to them is likely to be as critical to the eventual success of microbicides as was our response to the scientific challenges and political challenges of the recent past.

This change in terrain has come about for three main reasons. First, the scientific research that mostly involved lab and animal research in the 1990s has now moved to human communities in the first decade of the 21st century. We are no longer discussing results on microscope slides, but effects on real human beings. Microbicide candidate products now need to be tested—not only by women in general, but the women who most urgently need them: primarily poor vulnerable women in developing countries.

Second, a dramatic drop in cost for antiretroviral drugs and a growing demand by developing-world citizens for access to treatment has redefined expectations and hopes with respect to access to HIV care. This in turn has kindled debate on access to HIV treatment in the context of prevention trials.

And finally, recent controversies over the design and conduct of clinical trials of oral tenofovir have highlighted how difficult prevention trials can be, and how essential transparency and ethics are to building community trust.[3] Two trials—one in Cambodia and the other in Cameroon—have already been halted in response to activist and community concerns regarding trial ethics. Unless dealt with proactively, ethical quandaries could delay or derail a generation of future trials.

The International Consultation on Ethical Issues in the Testing of Microbicides, October 2003

On October 23–24, 2003, the Global Campaign for Microbicides brought together 64 people from 12 countries to rethink the issues and ethical dilemmas facing the field of microbicide development. The Consultation comprised a broad range of stakeholders, including advocates, ethicists, clinical investigators, community members, drug regulatory authorities, and past participants in microbicide clinical trials. (See Appendix A: Participant List.)

The purpose of the Consultation was to provide a forum for deliberation, taking on some of the toughest ethical questions in the conduct of clinical research on microbicides. What is an appropriate balance of risks and benefits for those who participate in trials? What constitutes meaningful (versus nominal or legalistic) informed consent? Should trials enroll adolescents under 18 years old? To what extent should male partners be included in the research process? Should partner consent be required? What is the appropriate ethical line between fair compensation and undue inducement? Should sponsors be obligated to guarantee antiretroviral therapy (ART) to those who become HIV positive during the trial? And looking to the future, what does finding a

[3] Tenofovir is an existing drug used for HIV treatment that is currently being tested as a possible once-a-day prophylactic pill to prevent HIV transmission among healthy individuals. For more on the oral tenofovir trials see: The trials of tenofovir trials. *The Lancet*. 2005; 65(9465):1111.

AIDS Vaccine Advocacy Coalition. Will a Pill a day prevent HIV? Anticipating the results of the tenofovir "PREP" trials. New York: AVAC; 2005. Available at: http://avac.org.phtemp.com/pdf/tenofovir.pdf.

partially effective microbicide mean for the design of the next generation of microbicide trials?

The organizers of the Consultation hoped to shed light on the ethical and practical dilemmas faced by communities, investigators, donors, research institutions, and host governments as they proceed with large-scale clinical trials on microbicides. (See Appendix B: Consultation Agenda). The goal was not to render judgments but to offer insights and to expand the range of actors involved in the deliberation of these important issues. In keeping with this spirit, the consultation was preceded by a daylong training session in ethical reasoning to help prepare participants to participate fully in all discussions. The course—now being offered more widely by the Global Campaign for Microbicides—includes background information on prevention trials, an introduction to ethical principles and reasoning, and several applied case studies. (See Appendix B for more details).

Roots of the Consultation

The decision to organize the 2003 Consultation was rooted in a history of earlier deliberations and motivated by developments in the HIV prevention research field. In April 1997, the Women's Health Advocates on Microbicides (WHAM)[4] and the Population Council jointly sponsored a symposium, "Practical and Ethical Dilemmas in the Clinical Testing of Microbicides." That symposium anticipated—and began to concretely address—some of the thorniest dilemmas in the clinical testing of HIV-prevention products, particularly microbicides. As shown in Box 1, the symposium report offered a number of important ethical recommendations, based on the points of greatest concern and consensus during that meeting.[5] (See Box 1, Recommendations from the 1997 Ethics Consultation on Microbicide Trials).

Since 1997, several microbicide and HIV vaccine trials have gone into the field, providing first-hand experience to inform the ongoing ethical discussion. Moreover, a number of controversies around the ethics of HIV-prevention trials have helped to stimulate wide-ranging, often heated debates.[6] UNAIDS has convened a series of meetings on ethical challenges in the clinical testing of HIV vaccines—many of which parallel those in the microbicides field. And the HIV Prevention Trial Network (HPTN) has formed an International Ethics Working Group and issued it own ethics guidance document.[7]

These discussions have drawn in many new actors and helped to broaden and deepen the debate on these issues. At the same time, the dramatic decrease in the cost of antiretroviral therapy (ART) has altered the

[4] The Women's Health Advocates on Microbicides (WHAM) was a group of 12 women's health networks that collaborated between 1993 and 1997 to influence and guide the microbicide development program of the Population Council. In 1998, WHAM officially disbanded and reorganized into today's Global Campaign for Microbicides.

[5] Heise L, McGrory CE, Wood S. *Practical and Ethical Dilemmas in the Clinical Testing of Microbicides: A Report on a Symposium*. New York: International Women's Health Coalition; 1998.

[6] For an introduction to on-going ethical debates see: Weijer C, Anderson JA. The ethics wars: disputes over international research. *Hastings Center Report*. 2001; 31:18–20.

[7] HPTN Ethics Working Group. HIV Prevention Trials Networks Ethical Guidance for Research. Arlington, VA: HPTN; 2003. Available at: http://www.hptn.org/ResearchEthics/HPTN_Ethics_Guidance.htm.

BOX 1. Recommendations from the 1997 Ethics Consultation on Microbicide Trials

General Recommendations on Clinical Testing of Microbicides

- Microbicide research and development should be embedded in a larger commitment to address the full range of factors that place individuals at risk of sexually transmitted infections.
- Social science research is critical to informing the design of trials, interpreting results, and answering key questions related to formulation and product introduction.
- Clear and transparent mechanisms should determine which products get access to publicly funded trial infrastructure.
- Issues of access must be addressed now, so that any future microbicides are available to and affordable for those who need them most.

Site Selection, Participant Enrollment, and Host-Country Relations

- Trials should be multisite in both the North and the South, in order to share the burdens and benefits of research and to increase the applicability of the results to different populations.
- Ideally, the selection of trial sites should reflect a careful weighing of scientific, ethical, and political imperatives, following full consultation with host-country governments, research sponsors, and local communities and advocates.
- The principle of distributive justice demands that all reasonable efforts should be made to include sites from the United States and Europe in any global effort to evaluate the efficacy of topical microbicides.
- Investigators and trial sponsors should place more emphasis on enrolling non-sex-worker populations in microbicide efficacy trials.
- Researchers and product developers should investigate a product's safety and effect on women who are infected with HIV.
- Microbicide clinical trials, particularly their exclusion criteria, must be designed by researchers and understood by the community to protect the confidentiality of participants' HIV status.
- Research collaborations should be cognizant of the historical imbalance in power that derives from the inequalities in resources and infrastructure between individuals and institutions in the North and South.
- International investigators should respect and seek to enhance host-country regulatory mechanisms for research.

Appropriate Standards of Care

- Investigators have an ethical responsibility to actively and conscientiously encourage all trial participants to use condoms in addition to the test product (or placebo) during each act of intercourse.
- To minimize real or perceived conflicts of interest, investigators should consider partnering with other entities to conduct a trial's risk reduction intervention.

- Investigators should either provide services to treat sexually transmitted infections discovered during the trial or arrange to refer participants for treatment.
- Community consultation and social science research can and should help to determine what services and interventions are appropriate as part of a trial within each local context.
- Investigators should establish and maintain formal relationships with NGOs and other sources of AIDS–related health care in the community.
- Studies should be prepared to provide HIV counseling and referral for HIV positive individuals.
- Wherever possible, trial sponsors and investigators should strengthen local health and laboratory resources rather than establish services that will "disappear" once the trial is complete.
- Investigators must develop clear policies for handling women who become pregnant during the trial.

Informed Consent

- International guidelines for the ethical conduct of research require a thorough and meaningful informed consent process to ensure that each individual's participation is voluntary. Informed consent is a process, not simply the act of signing a form.
- Study organizers must present the information in a language and manner that potential participants can fully understand.
- Researchers must provide potential trial participants with all relevant information necessary for making a decision.
- Each individual's decision must be fully voluntary, without undue influence or implicitly coercive incentives.
- Trial protocols should include formal mechanisms to remind participants that they can withdraw at any time.
- Ideally, each trial should have an independent community advocate to receive complaints, resolve concerns, and answer questions.
- Investigators should not substitute community or household consent for explicit consent by the woman who will participate in the trial.
- Investigators should think carefully before requiring the consent of the male partners of women participating in Phase 1 and 2 safety trials. Partner consent should not be sought in Phase 3 efficacy trials.

Maximizing Community Involvement

- Genuine community involvement is essential for ethical, scientifically sound research.
- Research agencies involved in developing clinical trial infrastructure should be committed to community consultation at all sites. They should look to social scientists and advocates to help carry this out appropriately and effectively.
- Trial sponsors should hold public forums—at both local and national levels—to discuss the ethical, scientific, and social issues accompanying trials.
- Consultation on trial implementation and ethics should include input from individuals who share the characteristics—class, race, gender—of the study participants.

(The full report is available from: *http://www.global-campaign.org/researchethics.htm)*

discourse on provision of ART to trial participants and to their communities. When WHAM held its first ethics consultation the issue of access to ART was not even on the agenda. Finally, with the possibility of a second generation of microbicides on the horizon, a completely new range of ethical problems will need to be addressed. As one of the Consultation participants observed, "The ground has been moving under our feet for the last five years."

The Global Campaign for Microbicides organized this meeting in hope of creating a "roadmap for deliberation" over the roughest spots of the present and future ethical terrain. This report summarizes some of the most significant presentations and discussions. It is intended not only to capture the richness of ideas but also to bring new tools and insights to those who will grapple with the ethical as well as scientific challenge of bringing microbicides to life.

2. Background: How Microbicides Are Developed and Tested

As with any new health technology or drug, candidate microbicides must pass through a series of rigorous tests to determine their safety and efficacy. These tests start in the laboratory, where researchers determine whether a compound fights HIV and sexually transmitted disease (STD) pathogens, first in test tubes and then in animals. If the data from these trials show that the product is potentially effective and relatively safe (non-irritating) in animals, then clinical (human) trials can begin.

Determining safety and effectiveness through clinical trials

There are three phases of clinical trials. Phase 1 trials determine the safety of the product when used by a small number of healthy, low-risk women over a few weeks. Phase 2 trials also test for safety of the product, but over a longer time and with a larger number of women, some of whom may have higher risk factors. Some preliminary data about efficacy and acceptability of the product may also be collected. Phase 3 trials enroll thousands of people in several sites. The trials measure effectiveness—that is, whether or not the microbicide actually works to prevent HIV and STDs.

Microbicide candidates generally proceed through a series of Phase 1 safety trials for different user groups before moving on to effectiveness testing. If a candidate appears safe for low-risk women, additional Phase 1 trials are conducted to establish safety in heterosexual men, for HIV positive women and men, and sometimes for rectal use.

If safety is *not* demonstrated in early human trials, research on that candidate is stopped and the product is dropped from consideration as a potential microbicide. (See Box 2 for definitions of safety, efficacy, and effectiveness.)

Sixteen products with various targets and mechanisms of action are currently in

BOX 2: Safety, Efficacy, and Effectiveness in Clinical Trials

Safety refers to the absence of significant adverse events related to gel use in the study population. *Safety* does not mean "keeping participants *safe* from infection."

Efficacy is the maximum ability of a drug or treatment to produce a result. It represents the protection achieved if the drug is delivered and used correctly every time.

Effectiveness is the real life ability of a drug or treatment to produce a result under conditions of "real use." It is measured as reduction in infections averaged across all users.

Note: Because not all trial participants in the active arm will use the microbicide every time, Phase 3 microbicide trials measure the effectiveness of a candidate microbicide, not its efficacy.

clinical trials in the United States and globally. It is crucial that several products with different mechanisms of action be tested simultaneously. This increases the probability and speed of finding a successful microbicide.

The differences between and among different kinds of products will greatly affect how they might be used and by whom. For example, some product concepts are based exclusively on enhancing the ecology of the vagina; others could potentially offer protection from rectal transmission as well.

Randomized clinical trials are the most reliable method of determining whether a new drug or intervention can be used safely by a large cross section of a population and whether it actually works. As shown in Figure 1, it normally takes about 10 years to move from a laboratory lead to a fully tested product that regulators deem safe and effective for human use.

How Phase 3 effectiveness trials are carried out

The critical Phase 3 effectiveness trials work by comparing two groups—those who receive the microbicide plus a standard prevention package (e.g., condoms, counseling, and STD treatment) and those who receive the standard prevention package plus a placebo gel. The placebo looks identical to the drug being studied but does not contain the active ingredient. Researchers randomly assign participants to one of the two groups, termed "arms." Randomization ensures that women in each arm are similar in every respect except the matter under study—the use of a test product versus a placebo. It should be emphasized that women are *never* deliberately exposed to HIV to see if the microbicide protects them. Instead, researchers compare the two groups to see whether the rate of HIV infection is lower among those who received the candidate microbicide with condoms compared with those who received condoms and a placebo. The difference is considered to be a measure of the candidate microbicide's effectiveness.

All trial participants receive intensive condom counseling; free, high quality condoms; and regular treatment for STDs. Women are actively encouraged to use condoms whether or not they are given the active microbicide candidate. As shown in Table 1, several thousand women must participate in a Phase 3 trial in order to determine whether a reduced HIV infection rate can be attributed to the microbicide.

FIGURE 1: Timeline to Develop and Test a Microbicide Product

Source: *Global Campaign for Microbicides*

TABLE 1: Clinical Trial Phases—Number of Participants, Length, and Purpose

	Number of participants	Length of treatment and follow up	Purpose
Phase 1	25-40	1 to 4 weeks	To assess local and systemic safety and acceptability, and to determine dose and formulation. May run into a Phase 2 trial (called Phase 1/2).
Phase 2	200-400	2 to 6 months	To assess safety and acceptability among higher-risk women over a longer time.
Phase 2b	500-3000	6 months to 2 years	To screen for products reaching a minimum level of effectiveness. Smaller, less costly than Phase 3, but numbers of participants and length of follow-up indicate whether a subsequent larger trial would be worthwhile. If so, participants sometimes continue from one trial to the next, and additional participants are recruited (such trials are called Phase 2/3).
Phase 3	3,000-10,000	2 to 4 years	To evaluate effectiveness in preventing HIV infection and other STDs and to assess long-term safety and acceptability. Some Phase 3 trials will involve multiple products, which will require more participants than those testing only one product.

Note: Phases 1/2, 2/2b, and 2/3 are variants of study designs or studies that move from one clinical trial phase to the next. The number of participants and length of treatment and follow-up vary.

Source: Table adapted from Upadhaya U. *Microbicides: New Potential for Protection*. INFO Reports No. 3. Baltimore, MD: Johns Hopkins Bloomberg School of Public Health; 2005. Available at: http://www.infoforhealth.org/inforeports/microbicides/microbicides.pdf

What microbicide products are being tested—how they work and what they do

Table 2 shows the five major microbicide products in Phase 2b or Phase 3 clinical trials as of early 2005. Their mechanisms of action and characteristics differ significantly.

Participants generally do not increase their risk of becoming HIV infected by participating in a Phase 3 microbicide trial. Rather their risk is likely to decrease because the trial actively promotes condoms and provides treatment for STDs, which otherwise increase women's vulnerability to HIV. However, some women will nonetheless become infected during the trial because they are still unable to negotiate consistent condom use with their partners. Among these cases, Phase 3 effectiveness trials measure whether the active microbicide product offers any protection over and above standard prevention.

Table 3 shows the developers and principal trial investigators for the five main microbicide candidates in effectiveness trials as of early 2005 as well as the phase and location of these trials.

TABLE 2: Microbicides Entering Effectiveness Trials

Microbicide name	Mechanism of action	Description	Potential pregnancy prevention?	Potential STD/HIV protection*
BufferGel (Carbomer 974P)	Vaginal defense/ acid buffer	Polymer gel reinforces vaginal acidity by acidifying the ejaculate.	Yes	HIV, chlamydia, herpes, HPV, gonorrhea
Carraguard (PC-515)	Attachment inhibitor	Carrageenan (derived from seaweed) binds to block viruses from attaching to and infecting healthy cells.	No	HIV, Herpes, HPV, gonorrhea
Cellulose sulfate	Attachment inhibitor	Binds to viruses and bacteria to prevent them from attaching to and infecting healthy cells.	Yes	HIV, gonorrhea, chlamydia,
PRO 2000 (Polynaphthalene sulfonate)	Entry and fusion inhibitor	Binds to viruses and bacteria to prevent them from attaching to and infecting healthy cells.	Yes	HIV, gonorrhea, herpes
Savvy(C31G)	Surfactant	Detergent disrupts viral, bacterial, and cell membranes, including those of sperm.	Yes	HIV, chlamydia, herpes

*As demonstrated in animal models.

Source for potential STD/HIV protection: Zeitlin L. and Whaley K.J. Microbicides for preventing transmission of genital herpes. Herpes. 2002;9(1):4-9.

(For more information on these and other candidate products, see the Alliance for Microbicide Development's website www.microbicide.org or the Global Campaign's Trials Watch, Factsheet #13, at www.global-campaign.org/download.htm.)

Figure 2 shows the location of all communities that have participated or are participating in clinical trials of microbicides. The map illustrates that microbicide trials are taking place in both the industrial and developing world. Most of the trials in the United States and Europe are Phase 1 safety trials rather than Phase 3 effectiveness trials. Microbicide trials must be mounted among populations at high risk of acquiring HIV who do not use injecting drugs or engage in other HIV risk behaviors besides vaginal intercourse. (If a woman uses injecting drugs, it would be impossible to know whether an infection is due to sharing of needles or a failure of the experimental products). Populations that fit this description are mostly in the developing world.

Protecting the human rights of participants during trials

Before a trial can proceed, a national and/or local ethical review board must approve the trial protocol. These boards differ across the world, but their purpose is similar everywhere: to ensure that trials are scientifically valid and conform to prevailing ethical guidelines. Once a trial begins, a data and safety monitoring board (DSMB)

TABLE 3: Developers, Investigators, and Status of Trials, by Candidate Product

Candidate product	Developer	Trial investigator	When and where trials are happening
BufferGel (Carbomer 974P)	ReProtect LLC	HIV Prevention Trials Network	• Phase 2/2B—shared with PRO 2000 (.5% formulation). • Enrollment began February 2005. • Four-arm Phase 2b trial in which BufferGel will be compared to PRO 2000/5, a placebo gel, and a condom only arm. 3,000 participants will be enrolled in Durban and Hlabisa, South Africa; Lilongwe and Blantyre, Malawi; Moshi, Tanzania; Philadelphia, USA; Lusaka, Zambia; Harare and Chitungwiza, Zimbabwe.
Carraguard (PC-515)	Population Council	Population Council	• Phase 3. • Enrollment began in March 2004. • Two-arm study, standard prevention and microbicide compared to standard prevention and placebo gel. • Four sites in 3 centers: Pretoria, Cape Town, and Durban (South Africa). • 6,639 women will be recruited and followed at quarterly clinic visits for two years.
Cellulose sulfate	Global Microbicide Project	Family Health International CONRAD	• Phase 3. • Two separate trials, each is a 2-arm study, compared to placebo gel. • FHI is running a trial with 2,160 participants in Nigeria. Enrollment began in January 2005. • CONRAD is running a trial with 2,574 participants in Benin, Burkina Faso, India, South Africa, Uganda. Enrollment anticipated to begin in June 2005.
PRO 2000 0.5% formulation (Naphthalene sulfonate polymer)	Indevus Pharmaceutical, Inc.	HIV Prevention Trials Network	• Phase 2/2B-shared with BufferGel. • Enrollment began in February 2005. • Four-arm Phase 2b trial, in which PRO 2000 will be compared to BufferGel, a placebo gel, and a condom only arm. • 3,000 participants will be enrolled in Durban and Hlabisa, South Africa; Lilongwe and Blantyre, Malawi; Moshi, Tanzania; Philadelphia, USA; Lusaka, Zambia; Harare and Chitungwiza, Zimbabwe.

Table 3 continued on next page

TABLE 3: Developers, Investigators, and Status of Trials, by Candidate Product *(Continued)*

Candidate product	Developer	Trial investigator	When and where trials are happening
PRO 2000 0.5% and 2% formulation (Naphthalene sulfonate polymer)	Indevus Pharmaceutical, Inc.	Microbicide Development Programme	• Phase 3. • Three-arm study for two formulations (.5% and 2%) of PRO 2000. • Enrollment anticipated to begin in 2005 for 11,920 participants in South Africa, Tanzania, Uganda, Zambia. • This trial originally included dextrin-2-sulphate (Emmelle) but this product was excluded from the final design of the phase 3 trial.
Savvy(C31G)	Biosyn, Inc.	Family Health International	• Phase 3. • Enrollment began September 2004. • Two-arm study, compared to placebo gel. • A trial to assess its efficacy against HIV, supported by USAID and Family Health International. • 4,284 volunteers in Accra and Kumasi, Ghana; and Lagos and Ibadan, Nigeria.

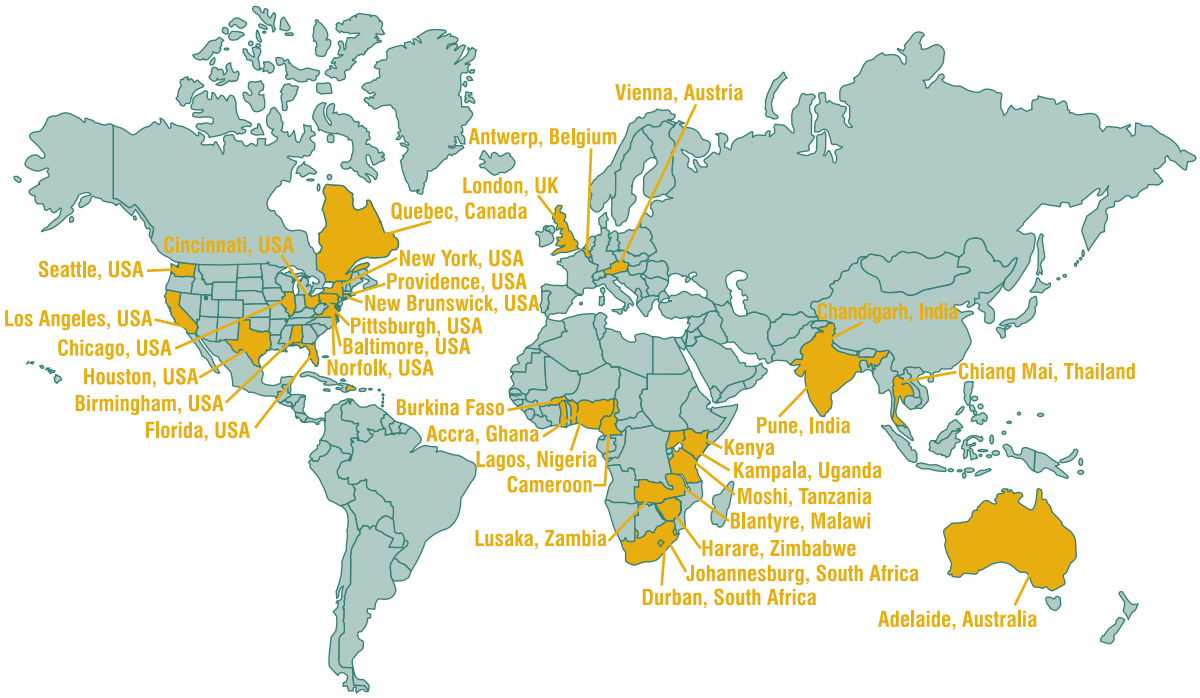
Source: Alliance for Microbicide Development

monitors the trial results in real time. This board has the authority to stop a trial if the test product appears to be definitely effective or ineffective. The "best case" scenario is for a microbicide's effectiveness to be so evident from early data that the trial can be suspended early, so that the product can be made publicly available to those who need it. This, however, has not yet occurred.

Many of the women who volunteer to participate in trials do not know their HIV status. Safety trials are conducted among both HIV-positive and HIV-negative participants, since products must be safe for both populations. However, Phase 3 trials can only enroll HIV-negative participants, because the rate of seroconversion among trial participants is the standard by which the effectiveness of the product is to be measured.

To be considered for trial enrollment, prospective participants must agree to HIV testing. Those who test positive are generally not enrolled in Phase 3 trials. Trials may exclude women for a wide variety of other reasons, including other health problems, a desire to become pregnant, or unwillingness to adhere to the trial protocol. In many communities around the world, people perceived to be HIV-positive face stigma and discrimination. For this reason,

FIGURE 2: Clinical Trial Sites (2005)



Source: Alliance for Microbicide Development

researchers and community groups must make clear that exclusion from a trial does not automatically imply that a woman is HIV-positive.

What happens to women who become infected during the trial?

The package of HIV prevention and treatment provided during the trial is referred to as the "standard of care." Within the microbicide field—and among Consultation participants in particular—everyone agrees that microbicide trials should improve upon the local standard of care—including HIV care. However, intense debate persists internationally over how the appropriate standard of care in international trials should be defined. This question is discussed in greater depth in subsequent sections of this report.

3. The Shifting Focus of Ethical Concern: From Thinking About Risks to Thinking About Benefits

Medical research ethics rest on three fundamental principles: first, autonomy and respect for persons; second, beneficence; and third, justice (Box 3).

Formal codification of research ethics dates back only 60 years, when outraged reaction to Nazi medical experimentation on human beings led to the Nuremberg Code of 1947. The Nuremberg Code and subsequent follow-up documents that provide ethical guidance on medical research have consistently focused on the first of these three principles—respect for persons. As discussed in the following chapter, concern for persons underpins the theory and practice of informed consent, the ethical issue that has received the greatest attention during the past half century. In contrast, the other two ethical principles—beneficence and justice—have received far less consideration. For those involved in rethinking the ethical roadmap for clinical testing of microbicides, particularly in developing countries, application of these latter two principles may pose an even greater challenge for those who wish to put ethical principles into practice.[1]

BOX 3: The Three Principles of Ethical Research

1. **Respect for Persons**
   At least two ethical convictions are incorporated in this principle—first, that individuals should be treated as autonomous agents; and second, that those with diminished autonomy are entitled to special protection. The notion of "informed consent" derives from this principle.
2. **Beneficence**
   The principle of beneficence creates the obligation to protect research participants from harm and to maximize possible benefits. It also leads to the notion that risks from the research must be commensurate with expected benefits.
3. **Justice**
   Justice is usually understood to mean that the benefits and burdens of research must be equitably distributed.

The shifting focus: from abuse and risk to beneficence and distributive justice

From early emphasis on the protection of human research subjects, the ethical debate has shifted to focus on the benefits that trial participants receive and the broader implications for distributive justice. This shift began in the 1980s. In response to the growing HIV epidemic, AIDS activists vigorously demanded broader access to potentially life-saving drugs, even those still considered to be experimental. In the 1990s, feminists in the United States increasingly joined in common cause as they protested women's historical exclusion from

[1] IJsselmuidden, C. Some ethical aspects of HIV/AIDS prevention trials: Protecting subjects against research risks and ensuring a fair distribution of potential research benefits. Background paper commissioned for: Practical and Ethical Dilemmas in the Clinical Testing of Microbicides, April 27-30, 1997; Warrenton, Virginia.

clinical trials—a reality that in effect denied women trial benefits. These developments first came to the forefront as political issues in developed countries; but their practical ramifications soon spread, and they have helped to reshape clinical research around the world.

Initially, the priority was to rethink the risks and benefits that could and should be expected by individual participants. Discussions focused on the quality and type of health care the trial provided individuals. Yet research also offers benefits at the collective level—to research institutions, host governments, and communities. Collective benefits might include improved health care services and infrastructure, and access to diagnostic tests, information, and training. Given this second kind of potential, attention has gradually shifted from individual to community-level benefits. This shift has brought the third principle of ethical research, the question of justice, more sharply into focus.

Consideration of distributive justice requires a different set of questions—in particular, who receives (or more to the point, who should receive) the specific goods within a total benefits package. This perspective requires weighing benefits, at both individual and collective levels, against the burden of risk and then finding the balance of short- and long-term benefits for respective stakeholders.

In reframing such questions, the general trend has been to rely far more directly upon consultation with the individuals and the communities who are directly affected. Typically, clinical researchers now turn to social scientists, nongovernmental organizations, and community-based organizations. They solicit input from both individuals and communities to help prioritize benefits that contribute more broadly to justice. Inevitably, new questions arise on the ethics of the process: Who represents and speaks for the community? What precisely qualifies as "input"? What is meant by "involvement"? And ultimately, who decides when tradeoffs must be made?

Evolving ethical guidance

With this shift in focus, ethical debate has continued to evolve. Several bodies have recently updated their guidance documents on clinical research ethics. As shown in Table 4, these include the Council for International Organizations of Medical Sciences and the World Medical Association (authors of the Declaration of Helsinki). Other entities have issued new guidance, including the Council of the European Union. Still others have issued specialized documents to interpret existing guidance (e.g., the Nuffield Council on Bioethics), to guide their own constituents (e.g., the UK Medical Research Council[2] and the National Institutes of Health),[3] or to offer interpretations in a specific area, such as HIV prevention (e.g., HPTN) or vaccine research (e.g., UNAIDS).

This deepening debate has raised vexing questions on who is to determine the balance of risks versus benefits and on what basis. One response, beginning in the 1980s, has been to require ethics training for

[2] UK Medical Research Council (MRC). Ethics Guide: Research Involving Human Participants in Developing Societies. London: MRC; 2003.

[3] National Institutes of Health (NIH); Guidelines for the Conduct of Research Involving Human Subjects at NIH; 1997. Fifth printing, Washington DC: NIH; August 2004.

TABLE 4: Key Ethical Guidance Documents

Document	Status	Source
World Medical Association (WMA) Since first published in 1964, the Declaration of Helsinki has been generally regarded as the preeminent guidance on the ethics of research related to health care. It has been revised five times by the WMA, most recently in 2000. Paragraphs 29 (Standard of Care) and 30 (After the Research) were discussed and clarified in 2002 and 2004 respectively.	Not legally binding, but frequently referred to in other forms of guidance and regulation	World Medical Association (Declaration of Helsinki), 2000. Ethical Principles for Medical Research Involving Human Subjects. Available at http://www.wma.net/e/policy/b3.htm
The Council for International Organizations of Medical Sciences (CIOMS), in collaboration with **World Health Organization** In 1982, CIOMS, published *International Ethical Guidelines for Biomedical Research Involving Human Subjects,* which addressed the special circumstances when applying the Declaration of Helsinki to research in developing countries. The CIOMS guidelines were revised in 1991, 1993, and 2002.	Not legally binding	CIOMS, 2002. International Ethical Guidelines for Biomedical Research involving Human Subjects. Available at http//www.cioms.ch/frame_guidelines_nov_2002.htm
European Parliament and the Council of the European Union Directive 2001/20/EC relates to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, April 2001. Adopted by member states by May 2003; brought into force, May 2004.	Incorporated into national law for EU member states; applies within the EU and for multicenter clinical trials taking place in member states and other countries	Directive 2001/20/EC of the European Parliament and of the Council. See http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf
Steering Committee on Bioethics of the Council of Europe Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, adopted by the Committee of Ministers, June 2004.	Legally binding if signed and ratified	Protocol to the Convention on Human Rights and Biomedicine. Available at http://conventions.coe.int/Treaty/EN/Projets/Protocol-Biomedical%20research.htm#
The European Group on Ethics in Science and New Technologies (EGE) Opinion No. 17 on the ethical aspects of clinical research in developing countries, published on February 4, 2003.	Advisory	Opinion No. 17. Available at http://europa.eu.int/comm/european_group_ethics/docs/avis17_en.pdf

Document	Status	Source
Office of Human Research Protection (US Health and Human Services Department) 45 CFR 46. Provides ethical regulations for all research involving human subjects conducted or supported by the US government, including research outside of the United States.	Legally binding on US-sponsored research	Code of Federal Regulations/ Part 46: Protection of Human Subjects. Available at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm
Nuffield Council on Bioethics In April 2002, the Nuffield Council issued *The Ethics of Research Related to Healthcare in Developing Countries.* This document does not provide specific guidelines; but it attempts to establish an ethical framework for those conducting such research, and it provides recommendations. An updated paper was issued March 17, 2005.	Advisory	Nuffield Council on Bioethics: The Ethics of Research Related to Healthcare in Developing Countries, April 2002; updated March 2005. Available at http://www.nuffieldbioethics.org/go/ourwork/developingcountries/page_246.html
UNAIDS After extensive consultation on four continents, UNAIDS published *Ethical Considerations in HIV Preventive Vaccine Research* in 2000.	Advisory	UNAIDS, 2000. Ethical Considerations in HIV Preventive Vaccine Research. Available at http://www.unaids.org/html/pub/publications/irc-pub01/jc072-ethicalcons_en_pdf.htm
HIV Prevention Trials Network (HPTN) *Ethics Guidance for Research,* issued April 15, 2003.	Advisory	HPTN, 2003. HIV Prevention Trials Network Ethics Guidance for Research. See http://www.hptn.org/HPTNResearchEthics.htm

researchers in order to internalize ethical reasoning into research design. In addition, formal ethics review boards are used increasingly to review and approve biomedical research involving human beings. In recent years, both ethical review boards and capacity building in ethics has come to be more commonplace in the Global South, where more and more clinical research on human populations is now taking place.

Ethicists from the US NIH recently set new benchmarks for ethical research in developing countries, highlighting the need for collaborative partnership, social value, scientific validity, fair selection of study populations, favorable risk-benefit ratio, independent review, informed consent, and respect for recruited participants and study communities.[4] This framework provides an important new articulation of research ethics, though many pressing questions remain unanswered: Who determines social value and scientific validity? And most importantly, who is seated at the table when such judgments are made?

Most current conceptualizations of research ethics derive from Western traditions in religion and philosophy. Recently, developing country ethicists have begun to articulate their own notions of research ethics,

[4] Emanuel E, Wendler D, Killen J, Grady C. What makes clinical research in developing countries ethical? The benchmarks of ethical research. *Journal of Infectious Diseases*. 2004;189:930–937.

sometimes challenging and sometimes endorsing prevailing constructions. The capacity of less- developed countries to articulate and argue their own perspectives is increasingly threatened by efforts of drug regulators and the pharmaceutical industry to harmonize testing and approval procedures for new pharmaceutical drugs. This effort is being spearheaded by the International Conference on Harmonization of Technical Requirements. Driven largely by the needs of the US, European, and Japanese drug industry, it seeks a single standard to which all drug testing would conform. To challenge such trends, the voices of a broader range of stakeholders will need to be heard in upcoming global dialogue on research practice and ethics.

Ethical deliberation

During the 2003 International Consultation, considerable intellectual tension surfaced on whether ethical standards should or could be moderated in the interest of science for the public good. Should scientific standards sometimes be compromised in order to preserve the highest standards of ethical integrity? Some Consultation participants justified selective infringement on ethical ideals where not doing so might compromise socially beneficial scientific research or undermine the overall credibility and usefulness of a scientific study. Some pointed out that research that is *not* scientifically sound is itself unethical, because it exposes individuals to burdens or risk without providing clear answers to the question under study. Others argued that scientific progress must occasionally be set back in order to maintain ethical standards, especially since scientific priorities are seldom purely objective, much less democratically determined.

Participants recognized that not every ethical argument carries the same weight. The real work of ethics is to make reasoned judgments by balancing the principles. Consultation participants agreed that measures to reduce harm and maximize good must always be taken as the starting point. Yet rigidity is no friend to ethics. The capacity to balance wisely among competing claims and potential opportunities is by far the harder part of the thinking and doing process. The problem is not whether "to do good," but how to allocate limited resources for the greatest overall social benefit in particular situations.

Consultation participants strongly reiterated the continuing need to protect individuals from potential risks in trials. Yet for those involved in clinical microbicide trials, the distribution of benefits—as expressions of beneficence and justice—is perhaps an even harder challenge. To act responsibly, the field of research ethics must first embrace a wider spectrum of actors and perspectives.

Finally, several participants suggested that adopting a human rights perspective might provide a useful complementary framework for thinking about the conduct of ethical research. In addition to the three mainstay ethical principles—respect for persons, beneficence, and justice—the practice of human rights focuses attention on rights to health, information, and bodily integrity. More work should be done to explore the utility of human rights norms and mechanisms to improve medical research practice.[5]

[5] Faunce TA. Will international human rights subsume medical ethics? Intersections in the UNESCO Universal Bioethics Declaration. Journal of Medical Ethics. 2005;31:173–178.

4. How Informed is Informed Consent?

Among issues of research ethics, informed consent has historically received the greatest attention. Nonetheless, a significant gap persists between the spirit of informed consent and what it actually means in practice. Ideally, informed consent would reflect an agreement between researcher and participant, entailing ongoing dialogue to improve the conduct of research. Yet in reality, informed consent is often something far different—largely a series of legalistic measures to conform to regulatory requirements. Too often, informed consent is a one-way, one-time communication, a hurdle so that researchers can move on to the next stage of their research protocol.

Elements of informed consent and emerging agreements

Agreement is widespread on the principal components of informed consent: disclosure of information, comprehension, decision-making capacity, voluntariness, and an explicit declaration to participate or refuse.[1] Historically, informed consent has emphasized disclosure, especially in the United States where informed consent is often driven by fear of litigation. As a matter of self-protection, researchers and sponsors provide mountains of information, which may or may not contribute to anyone's understanding of what participation actually entails.[2] Recent discussion has stressed the difference between information to improve the quality of participants' understanding and informational overkill to nominally cover bases.

Among Consultation participants and the ethical community, the critiques of informed consent have converged on several points of general agreement:

- Informed consent is a process, not a single action or moment in time.
- Emphasis should be on comprehension and choice, not merely disclosure.
- The amount of information should not be overwhelming or work against comprehension, and it must be conveyed in understandable language.[3]
- Persons who choose to consent need to take some explicit action to indicate their decision.
- Reimbursements should be appropriate to the setting and circumstances.

[1] Faden R, Beauchamp TL. A History and Theory of Informed Consent. New York: Oxford University Press; 1986.

[2] Research sponsored by the US Government must also conform to Health and Human Services regulations governing the protection of human subjects (46 CFR 45), which detail up to 14 elements of information that must be imparted to participants during the informed consent process.

[3] The amount and nature of information should be sufficient so that a "reasonable person" can weigh the risks and benefits of participation and make a fair decision. Exhaustive detail on pharmacology or research design is seldom essential to this process.

Informed consent as a process

Informed consent is a process with multiple stages and multiple levels that requires ongoing effort and renewal.[4] In microbicide trials, informed consent begins at an early stage with community education about HIV and the nature of the proposed research. With that said, one Consultation participant also cautioned that "community education" can easily veer across the line into marketing and recruitment. Educating does not mean selling. Individual prerogative is not served if a village chief or church leader decides to sanction a trial, thereby pressuring some community members to join.

Informed consent should be phased. The explicit action that indicates consent should not be required when the information is provided. Participants should be able to absorb, think about the information, discuss it with friends and family, ask questions, and then return with a decision.

Community consultation

Most terminology used in research—including the notion of research itself—is unfamiliar and not easy to translate in the typical settings where HIV prevention research takes place. Serious community consultation provides the basis for communication, first by helping researchers to understand how a community interprets rarefied concepts such as confidentiality and free choice. With discussion and patience, a community can find its own terminology to interpret and explain the study concepts, thus making individual consent meaningful.

Confidentiality

Confidentiality on who is and isn't participating in the trial is utterly essential, especially if community pressure develops either against or in favor of the study. Generally, only HIV-negative women can be enrolled in a Phase 3 microbicide effectiveness trial. Being "screened out" can therefore imply a serious message about a woman's serostatus to friends, family, and male partners. If others interpret being screened out to mean that a woman is probably HIV-positive, the negative consequences can be severe. Thus, every effort must be made not to signal who is participating—for example, if blood is drawn from those who test HIV-negative, even those who are HIV-positive should leave the test location with a bandage on their arm.

Ensuring understanding

At the time of enrollment, participants should consent individually. Several methods can improve and confirm each person's understanding of what's involved—for example, the use of check lists, focus groups, exit interviews, flip charts, and videos. In response to participants' suggestions from a Phase 2 trial in South Africa, the Population Council produced a video for its Phase 3 trial. The video explained difficult concepts in a dynamic, graphically appealing fashion. The Medical Research Council (MRC) has similarly adapted materials across sites—flip charts in South Africa, a video in Uganda, and discussion groups elsewhere.

Comprehension tests should be repeated from time to time, with participants being periodically asked to reaffirm their consent. The HPTN has developed a preenrollment bank of questions for all prospective participants. As the trial unfolds, researchers draw upon the questions to

[4] Woodsong C, Abdool-Karim Q. A model designed to enhance informed consent: Experiences from the HIV Prevention Trials Network. *American Journal of Public Health*. 2005; 95(3):412–419.

retest a sample of participants. Other research institutions pose questions to participants at regular intervals—for example, every three months.

Consultation participants agreed that qualitative and quantitative methods each offer advantages and can be combined. Open-ended questions allow women to speak in their own language. The point is whether a woman understands key concepts, not whether she can repeat language verbatim from consent forms. Research staff can use open-ended questioning along side a checklist that probes for comprehension. When a participant fails to touch upon an important point, the researcher can ascertain understanding by posing additional questions on that topic.

It is not always clear how to proceed if a participant apparently does not understand all the information that investigators and ethicists deem as appropriate. Should she be encouraged to withdraw, or at least be strongly reminded that she can do so? Or should the information be provided again but in a different way?

More training of research teams and new approaches to conveying sophisticated information are clearly required. Hard data on the quality of informed consent in prevention trials is scarce. Most importantly, research sponsors and investigators must commit to conducting exploratory research prior to trial initiation to guide the process of informed consent. Experience is proving that informed consent in HIV prevention trials will not be achieved without concentrated effort to identify which words, concepts, and communication techniques make sense locally.

Admittedly, pretrial research on informed consent and ongoing monitoring is yet another expense that adds to the cost of trials. Yet for sponsors and researchers, there are tangible benefits beyond the obligation to meet ethical standards. If carried out well, the process of informed consent helps to minimize participant dropout. Moreover, a high-quality informed consent process improves overall adherence to the trial regimen and thus produces better data in the end.

5. What to Do About Male Partners?

Some of the most difficult questions related to informed consent revolve around male partners—in particular, should *they* be required to consent to their partners' participation in the research trial. Especially among women's advocates, the commitment to preserving—for that matter, to greatly strengthening—women's autonomy may run flatly at odds with cultural norms that grant decision-making authority to men.

At first glance, it may seem paradoxical to consider men's involvement, much less their consent, to test a product that allows disempowered women to protect themselves against men's pervasive unwillingness to negotiate condom use. In this regard, the 1997 Symposium, among other meetings, affirmed that *women's* consent is paramount and that women should determine if and how their male partners are to be involved.[1] Nevertheless, these are not open-and-shut questions. Men's safety, their eventual acceptance of microbicides, and their attitudes toward women's participation in clinical trials are highly relevant.

In considering what to do about male partners, it is important to distinguish among men's levels of engagement. Reaching out in the community to encourage men's support for clinical trials is one thing; requiring their consent for women to enroll is another. Similarly, assisting women to engage their male partners in a trial is quite different from accepting men's culturally reinforced "right" to decide for women regardless of their wishes.

Men's consent is legitimate and necessary to the extent that men may be exposed to an experimental product involving risk. However, this obligation can be addressed in several ways that respect women's autonomy. For example, safety of the product for penile exposure can be established early in the research process through men-only trials. Requiring male partner consent in Phase 3 clinical trials is not the only means of ensuring that products are safe for men.

The pros of involving male partners

There are many reasons to involve men in the clinical testing of vaginal microbicides. Among others, these include:

- All outcomes and effects of the products need to be studied and understood. This includes effects upon second parties as well as principal users.
- Partner safety is an unavoidable ethical issue, since men whose partners are participating in clinical trials will be exposed to vaginal microbicides during sexual intercourse without a condom, or possibly during oral sex.

[1] Heise L, McGrory CE, Wood S. *Practical and Ethical Dilemmas in the Clinical Testing of Microbicides*. New York: International Women's Health Coalition; 1998.

- Microbicide's acceptability to men will be critical to if and how women eventually use vaginal microbicides. Whether or not a product is capable of stopping HIV transmission, it will not be "effective" if men prevent women from using it.
- Involving men in microbicide trials may help to improve couples' communication, opening discussion on the question of HIV risk and protection.
- Male partners' active support would likely improve overall adherence to the study procedures and would encourage women to remain for the full duration of the study.
- Partners discovering women to be using the product without having informed them may become abusive or violent.

The cons of involving male partners

There are also good reasons *not* to involve men, and these too are compelling.

- Men's participation may reduce women's enrollment—men may refuse to allow women to participate, or women may decline because they do not want their partners to be informed or involved.
- Men's participation adds additional expense, complexity, and effort to conducting the trial. Moreover, many women may have more than one sexual partner.
- Men may further refuse to use condoms because they believe that the microbicide product now provides protection, which may expose both partners to greatly increased risk.
- Men may resist or hinder women's participation in the trial or their use of the product—for example, not allowing her to visit the clinic, taking the product away from her, or telling her that it is messy or decreases his sexual pleasure.

Engaging men too closely in the trial is ethically problematic if they pressure or coerce their partners to participate (or not), thereby infringing on her basic right to autonomy. The result could be disempowerment of women, precisely the opposite aim of microbicide development. A fundamental cornerstone of the microbicide agenda is that women must have control of the method and decide whether to inform their partners—or not.

Experiences from India and South Africa

Men are the principal decision-makers in many cultures; and whether or not their permission is explicitly required, their attitudes greatly affect women's participation. In many settings, women may find it unacceptable (or simply unthinkable) to participate without informing and involving their partners. Experience with field trials in many setting reveals that women typically *want* to include their partners in the research.

In India, observations of couples enrolled in an early Phase 1 safety trial revealed significant differences between men's and women's concerns and how they make decisions. During the informed consent process, women primarily worried about possible side effects. By contrast, men expressed many more concerns, including the amount of time that would be required and the possibility of lost wages related to study visits. They too expressed concerns over side effects, for themselves as well as their partners.

The rationale for participation also differed between men and women in India. Both groups were influenced by possible benefits, such as access to services, and by assurances that side effects would be appropriately treated. Both were also motivated by a larger sense of social responsibility. Men, however, were notably more influenced by the means through which they received information. If doubts emerged during the consent process, they often became quickly suspicious. For this reason, a detailed informed consent process was found to be essential in involving men. In contrast to women, men generally perceived far less need for a microbicide. Women discerned risk of HIV infection, and they understood the need for protection. Nevertheless, the *most* important factor influencing a woman's decision to participate was the approval from her male partner.[2]

Focus group research in South Africa revealed different issues related to male involvement. Men were concerned about women touching ("fidgeting") with their vaginas, and they worried about exposing their own genitals to the product. In a setting where men generally prefer "dry sex,"[3] men expressed concern that the product might be wet, messy, or interfere with their sexual pleasure.

The South African focus groups observed that men might find "subtle" ways to interfere with their partners' participation—for example, sending their wife to the rural areas "to look after the house or family," as one focus group member observed. On the other hand, concealing women's involvement could have worse repercussions, including violence. As one man put it, "If I find my partner using something in her vagina—that will be the day! This will mean that there is no trust in the relationship." In adherence with traditional law, a man might report a woman to community elders, who could pressure her not to participate, if not punish her.[4]

In both India and South Africa, the point was reiterated that involving men could increase men's sense of responsibility and their accountability. This applies not just to the study but extends to greater openness between partners in discussing safer sex practices. As with contraception, men often prefer that their partners take on the burden of using a method. Many men find the idea of a vaginal microbicide appealing for similar reasons, especially for sex with their regular partners.[5]

An emerging consensus on male participation

Despite strong encouragement to use condoms, some men will undoubtedly not do so. They will be exposing themselves to the product topically during Phase 3 trials—and to any harm that it might cause to them. It is therefore widely agreed that the safety

[2] Joglekar N. Involvement of men in vaginal microbicide trials: An Indian perspective. Presented at: International Consultation on Ethical Issues in the Clinical Testing of Microbicides, October 23-24, 2003; Warrenton, Virginia.

[3] In many parts of southern Africa, men are said to prefer "dry" rather than lubricated sex; and women routinely insert herbs or astringents to dry and tighten their vaginas prior to sex.

[4] Nkala B, Dickson K, Kubeka V. Male involvement in microbicide testing: Insights from South Africa. Presented at: International Consultation on Ethical Issues in the Clinical Testing of Microbicides, October 23-24, 2003; Washington DC.

[5] In India, many men said they would continue to use condoms in casual sexual relationships because they could not rely on unknown partners to use a microbicide.

of microbicides for men must be established before large-scale trials can be launched with women.

One option for establishing safety for men is to enroll couples in Phase 1 studies, which allows safety for men and women to be studied simultaneously. In addition to evaluating safety endpoints, male participants in Phase 1 vaginal safety trials could provide useful feedback on their experiences and attitudes toward the product. Researchers can use urine tests and visual exams to flag instances of penile irritation or inflammation that could be product related.[6]

Alternatively, researchers can mount separate male tolerance studies, which test whether the experimental product causes irritation to the penis or other negative side effects. In the microbicide world, male-only safety studies generally occur shortly after safety testing in women. They are repeated later in men who are HIV-positive and among men with other STDs to establish microbicide safety for these user groups. In early safety studies of this sort, men's consent is of course required.

In weighing the pros of involving men in microbicides trials—yet cognizant of the potential infringement on women's autonomy if men's formal consent is required—Consultation participants considered alternatives for Phase 2 and Phase 3 trials. One option would be to enroll only women who are comfortable including their male partners, despite the added complications to enrollment and possible dramatic reduction in the number of eligible women. This strategy could bias the study toward women in lower-risk relationships, possibly at the expense of fully representative data.

Most Consultation participants agreed that the involvement of men in Phase 2 and 3 trials is preferable, but that male partner consent should *not* be required. Depending on the specific characteristics of the trial, it may be appropriate and possible to enroll couples in earlier safety trials. Yet in the large-scale Phase 3 effectiveness trials, Consultation participants generally viewed requiring partner consent as neither practical nor desirable, especially since many women may have more than one sexual partner.

In summary, there are many good reasons to involve men in trials, but this stops short of requiring men's formal consent for women's participation. It is sufficient that women be encouraged to inform and involve their partners. Where women do choose to involve men, researchers should support their decisions by providing materials that are designed for men and by creating male-friendly clinic environments.

Further safety precautions for men

While Phase 1 safety trials should help to uncover serious safety issues for men, short-term safety trials may be inadequate for establishing longer-term safety among men who have sex more frequently. As a further precaution to enhance male safety, a "passive surveillance" system could be established to help capture any adverse events for men in Phase 2 and Phase 3 trials. In other words, researchers would ask women to refer men to the clinic with suspicious symptoms that could be product related. Whether or not men are actually

[6] A generic inflammation marker—urine leukocyte esterase—in the absence of an STD might indicate product-related effects.

enrolled in the trials, treating partners for these side effects should, of course, be part of the study protocol.

A more active alternative might be to test penile safety in higher-risk men by carrying out an ancillary study with men during or after the Phase 3 trial in women. Once a microbicide product is on the market, a post-approval surveillance system should also be established for reporting additional adverse effects.

Rectal use of microbicides

Regardless of its labeling, a microbicide that is marketed only for vaginal use is sure to be applied rectally by both men and by women. Studies have confirmed that anal sex is not uncommon among heterosexual men and women. One review of studies on the incidence of anal sex in sub-Saharan Africa found percentages among respondents ranging from 8 to 75 percent.[7] For this reason, advocates have long argued that it is important—both for men who have sex with men, and for heterosexual women and men who engage in anal sex—to establish whether products designed for vaginal use cause irritation or inflammation of the rectal mucosa. If that occurs, a considerable amount of effort must be invested in order to actively discourage rectal use of microbicides intended for the vagina.

Still under debate, however, is when rectal safety studies should be undertaken in the course of product development. Some argue that rectal safety studies should be pursued before a product goes into large-scale effectiveness trials for vaginal use among women. Although Phase 3 participants are routinely advised not to engage in anal sex—and explicitly, not to use the microbicide product rectally—they may do so anyway. This argues for establishing the rectal safety of vaginal products early on.

Others argue that it is sufficient to evaluate rectal safety once an experimental product demonstrates some effectiveness when used vaginally. Evaluating rectal safety earlier will require considerable expenditure of precious resources to test products that may not prove viable as vaginal products. Arguing from this perspective, the time between preliminary analysis of the data and regulatory approval should be sufficient to assess safety for rectal use.

Biologically, the rectum and the vagina are vastly different.[8] Regardless of when safety testing occurs, it is critically important to avoid any assumption among users that vaginal microbicides will be protective for anal sex. There can be no ambiguity allowing anyone to take for granted that a product meant for vaginal use will also protect when used rectally.

[7] Brody S, Potterat J. Assessing the role of anal intercourse in the epidemiology of AIDS in Africa. *International Journal of* STD *and* AIDS. 2003;14:431–436.

[8] The rectum and the vagina differ significantly in structure and natural ecologies. The vagina is a closed pouch while the rectum is part of an open-ended cavity. The rectal lining is more fragile than most of the tissue lining the vagina. It is also richer in CD4 receptors, cells particularly vulnerable to HIV infection. These factors further enhance rectal vulnerability to irritation, tearing, and infection during sex.

6. The Question of Enrolling Adolescents

What to do about teenagers?

Adolescents comprise a potentially large and extremely important group of prospective microbicide users. Traditionally, there has been much reluctance to involve adolescents in clinical trials, especially younger adolescents—and indeed, vexing questions make this matter exceptionally complex.

Adolescent girls differ from adult women both biologically and behaviorally. These differences potentially affect the effectiveness and, possibly, the safety of microbicide products. Such differences will likely affect whether, when, and how effectively adolescents can make use of future microbicides.

Our general wish to protect adolescents from research-related risks has a serious down side with respect to microbicides. As a result, we know far too little about the likely acceptability, safety, or efficacy of products among an alarmingly susceptible user group that is globally at great risk of infection. Fundamentally, the ethical question boils down to: Is there a compelling need to establish the safety and effectiveness of candidate products for younger adolescents as distinct from adult women; and if so, are these reasons sufficiently compelling to warrant the exposure of younger adolescents to research-related risks?

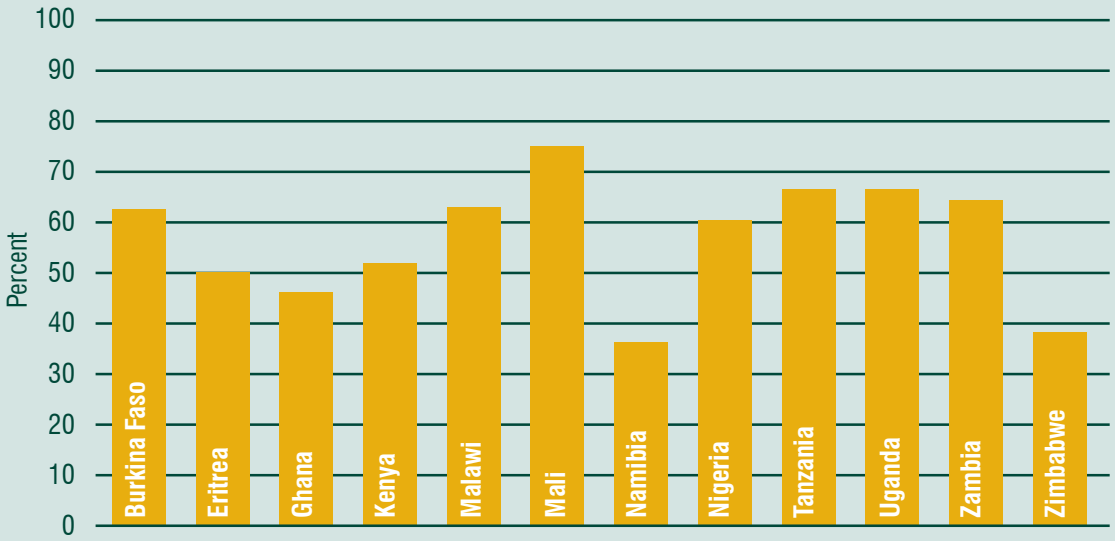
The Consultation broke down this dilemma into two interrelated questions. First, what are the behavioral and biological factors that could potentially alter the safety and effectiveness profile of microbicides in younger adolescents compared to older women? Second, what are the ethical, legal, and practical challenges if younger adolescents are to be enrolled in clinical trials?

Adolescent vulnerability

During adolescence, a young person's body and cognitive abilities develop rapidly. Hormonal changes are dramatic. The capacity to reason continues to evolve from the very concrete toward understanding of abstraction. By mid adolescence (normally around the ages of 14 to 16), most adolescents' cognitive abilities are roughly the same as biologically mature adults. Intellectually, they are able to understand issues such as long-term risks and the benefits of research. Yet there is another side to the coin. Adolescents of the same age are also frequently inclined toward risk taking, they are often resistant to adult advice, and they are acutely sensitive to peer influence. These factors can affect their understanding of risks and their capacity to make consistently sound judgments about their long-term best interest.

Young people around the world typically begin to engage in sexual activity during

FIGURE 3: Percentage of Women (ages 20-49) Who Had First Sexual Intercourse Before Age 18



Source: Demographic and Health Surveys, 1999-2003

these same years. In the United States, more than 60 percent of young women have had sex by the time they are in twelfth grade.[1] In sub-Saharan Africa, the percentage of women 15 to 19 who have had sexual intercourse ranges from 30 to more than 70 percent.[2] (Figure 3). Yet the percentage of 15- to 19-year-old women in sub-Saharan Africa who used a condom at their most recent sexual encounter is very low—well below 20 percent in all but two countries shown in Figure 4.[3]

Sexual exposure, together with the behavioral and biological realities of adolescence, combine to place young women at especially high risk of STDs, including HIV. In the United States, 15- to 19-year-olds have the highest rates of chlamydia and gonorrhea among women of all ages.[4] Rates of the human papillomavirus infection (HPV) are highest among women under the age of 21.[5] Young women and girls constitute nearly two-thirds of 15- to 24-year-olds living with HIV/AIDS in

[1] Centers for Disease Control and Prevention. Youth Risk Behavior Surveillance, 2003. In: Surveillance Summaries, May 21, 2004. *Morbidity and Mortality Weekly Report*. 2004; 53(No.-SS-2):1–100.

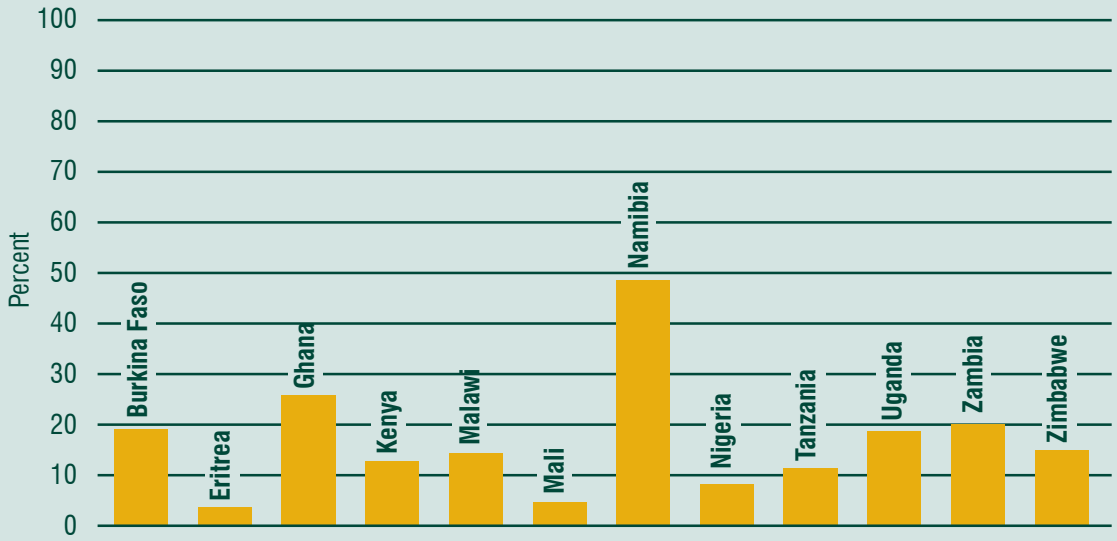
[2] Data from various Demographic and Health Surveys, Calverton, MD: ORC Macro International. Available at: http://www.measuredhs.com. Accessed March 21, 2005.

[3] Ibid. ORC Macro, 2005. MEASURE DHS STATcompiler. Available at: http://www.measuredhs.com. Accessed March 21, 2005.

[4] Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance*, 2003. Atlanta, GA: US Department of Health and Human Services, September 2004. Available at: http://www.cdc.gov/std/stats/03pdf/SFAdoles.pdf.

[5] Stone KM, et al. Seroprevalence of human papillomavirus type 16 infection in the United States. *Journal of Infectious Diseases*. 2002;186:1396–1402.

FIGURE 4: Percentage of Young Women (ages 15-19) Who Used a Condom in Their Most Recent Sexual Encounter



Source: Demographic and Health HIV/AIDS Survey Indicators Database, 1999-2003

developing countries. In some parts of sub-Saharan Africa, the infection rate of girls outnumbers that of boys by ratios of 6 to 1.[6]

Are adolescents sufficiently different from adults to warrant separate data?

Without doubt, adolescents represent a critically important user group for microbicides: Their behavior puts them at risk, and they bear a disproportionate share of the global health burden of STDs and HIV. But do those under 18 necessarily have to be enrolled in clinical trials? Is it reasonable and sufficient to extrapolate safety and effectiveness data derived from women over 18? If not, how should the microbicide community handle the ethical and legal challenges of enrolling younger adolescents in trials?

The Consultation sought out the expertise of Anna-Barbara Moscicki, associate director of the Division of Adolescent Medicine at the University of California San Francisco, to address the questions of biology and behavior. Dr. Moscicki argued forcefully that the biologic and behavioral differences between young adolescents and older women justify separate safety and effectiveness data on younger adolescents. As she explained, the cervixes of younger adolescents are not fully mature, making them biologically more susceptible to STDs. Adolescents' menstrual patterns also differ from adult women, as some 80 percent of adolescents will have cycles without ovulation within four years after menarche. Without ovulation, adolescents lack progesterone, which may influence the vagina's local immune responses. Box 4

[6] UNAIDS. *World* AIDS *Campaign* 2004: *Women, Girls,* HIV *and* AIDS. Geneva: UNAIDS; 2004.

BOX 4: Biologic Differences in Adolescent Versus Adult Women

In adult women, the inner neck of the cervical canal (known as the endocervix) is lined with single-cell columnar epithelium. The outer part of the cervix (ectocervix), which is exposed to STDs and other pathogens, is predominantly made up of a thicker, stronger squamous epithelium. In contrast, the fragile columnar cells of the endocervix extend down to the outer surface of the adolescent cervix (a condition known as ectopy), exposing this vulnerable region to trauma and pathogens via the vagina. The hormonal changes of puberty cause an increase in the acidity of the vagina and induce the columnar cells of the ectocervix to undergo a process known as metaplasia, which converts the fragile columnar cells into thicker, more protective squamous epithelium, thus helping safeguard the cervix from infections. This process, which takes several years, begins during puberty and is usually complete by the age of 24 or 25.

Adolescents' menstrual patterns also differ from adult women. Some 80 percent of adolescents will have cycles without ovulation within the first four years after menarche. Until they ovulate, adolescents lack progesterone. This may influence the vagina's local immune responses.

Before and during this metaplastic transition, a girl may be particularly vulnerable to infection. Columnar cells offer easier access to infection with the human papilloma virus, which then proliferates, stimulated by the process of metaplasia. A pubertal girl is also more vulnerable to chlamydia and gonorrhea, which preferentially adhere to the exposed columnar cells.

provides greater detail on some of these biological distinctions.

The behavior of younger adolescents also differs from adults in ways that could eventually affect how they will use microbicides. Such distinctions could become incredibly important when considering how to introduce and promote microbicides to teens.

Adolescents in clinical research

The prospect of including younger adolescents in research raises a tangle of legal, regulatory, and practical challenges.

In the first place, an essential tenet of ethical research is that participants must freely choose to participate. Those who consent (or whose consent is sought) must be able to understand the implications of information that is provided about the study.

Ethical guidelines have traditionally treated young people as "vulnerable," meaning their capacity to consent is limited and therefore requires special protection as a group. In the United States, for example, the code of federal regulations governing protection of human subjects does not distinguish between children and youth.[7] Both groups are considered "vulnerable"; and like pregnant women or prisoners, are afforded special protections in research. The National Bioethics Advisory Commission recently recommended that US regulations be updated to avoid rigid categorization of whole categories of people as vulnerable and in need of special protections.

The challenge is one of balance. There is tension between the desire to recognize the emerging autonomy of adolescents and the need to protect them. Their not yet mature response to personal risk must be

[7] Health and Human Services Regulations (45 CFR 46) entitled "Protection of Human Subjects."

recognized and weighed against the potential benefits from participation. Research involving adolescents must account for the particular characteristics of adolescents, including their tendency toward altruism, rebellion, and peer pressure, as well as their increased sensitivities around body image, privacy, and confidentiality.

The issue of parental consent

For federally funded research in the United States, adolescent participation in clinical trials requires permission from a parent or guardian, as well as the informed "assent" of the young person. Under specified conditions, local ethics review boards can waive the parental permission requirement. (No such waiver option exists in the federal regulations governing investigational research of the US Food and Drug Administration). Alternatively, they can require special accommodation.[8]

Parental permission requirements may create a barrier to young people's participation in clinical trials of microbicides. As explained in Chapter 2, individuals participating in Phase 3 trials must be at high risk of HIV infection. To protect their privacy, young people may choose not to participate in trials if they believe that their sexual activity may be disclosed to their parents. For researchers, this provides a challenge. They must creatively devise screening and consent procedures that protect young people's privacy while providing them with the benefits of being involved in research.

The US regulatory stance toward required parental permission is more restrictive than the position brought forward by the Special Programme on Research Development and Research Training on Human Reproduction (known as HRP) within the World Health Organization (WHO). HRP guidelines observe:

> There are no clear ethical justifications for excluding from research adolescent subjects below the age of legal majority. If there are reproductive health problems that are restricted to, or occur also in, adolescents that cannot be solved with existing knowledge, there is an ethical duty of beneficence and justice to conduct appropriate research to address these problems.
>
> Unless specific legal provisions exist, consent to participate in research should be given by the adolescent alone. Capacity to consent is related to the nature and complexity of the research. If adolescents are mature enough to understand the purpose of the proposed study and the involvement requested, then they are mature enough to consent.
>
> In such cases where adolescents are currently or are about to be sexually active, investigators commit no legal offence in undertaking research that promises a favourable benefit-risk ratio. However, where the law specifically denies decision-making authority to mature or competent adolescents below a given age, that provision must be respected (page 25).[9]

[8] In some cases where parental permission is waived—because there are no parents in the young person's life, or the parents are deemed unfit or incompetent—alternative means are established to protect the young person's rights. Where a study protocol requires adherence to a rigorous schedule, for example, adolescents may be provided special help to fulfill requirements.

[9] WHO Scientific and Ethical Review Group. *Guidelines for research on reproductive health of adolescents*. Geneva: WHO; 2000. Available at: http://www.who.int/reproductive-health/hrp/guidelines_adolescent.en.html.

Trials in developing countries

The codification of ethical requirements in most Southern countries is far less developed than in the United States or Europe. Botswana, for example, has no laws or regulations addressing adolescent participation in research. So the age of maturity—that is, the age at which a woman can legally sign a contract—is often used to exclude women under 21 from clinical research without parental consent. Yet the prevalence of HIV among 18- to 20-year-old pregnant women is 25 percent in Botswana, and nearly a quarter of the women at risk of HIV infection are 12 to 20 years old.[10] Excluding adolescents from microbicides research amounts to excluding a large percentage of the population at greatest risk.

The BOTUSA project, a joint initiative between the Botswana government and the US Centers for Disease Control and Prevention (CDC), is interested in enrolling younger adolescents in upcoming microbicide trials. To contextualize the issue, the project examined other kinds of laws and customs that define the age at which a young person in Botswana assumes adult roles and responsibilities. An 18-year-old, for example, can vote, operate a vehicle, purchase alcohol, or be tried for a crime as an adult. All adolescents may access family planning, be treated for an STD, or receive prenatal care without parental permission. A 16-year-old girl can legally consent to have sex, but she must be 21 to get an HIV test without parental permission or to enter into a legally binding contract.

In addition to the fundamental ethical question—the age at which most people are able to make sound judgments about participating in research—other reasons may dictate against involving adolescents without parental permission. For example, focus group research in Botswana revealed that enrolling adolescents without parental permission could alienate communities at the cost of losing support for the study. One proposal for enrolling adolescents *with* parental consent would be to recruit them into trials at postnatal care visits. With parents already aware that their teenage daughters have been sexually active, the researchers would ask parents for permission to screen the child for HIV (an eligibility criteria for microbicide trials), with the understanding that parents would not be apprised of their child's HIV status (unless the adolescent so wishes). The adolescent would make an autonomous decision on whether or not to enroll in the trial.

Constructing a way forward

Consultation participants agreed that establishing safety and effectiveness of microbicides among young adolescents is essential. Exactly how and when to collect this data, however, requires more in-depth consideration.

One approach would be to start with adults only in Phase 1 and 2 safety trials. Once a product candidate is shown to be safe for adults, combined Phase 1 and 2 trials could be undertaken with adolescents. If safety is confirmed, these young people could then

[10] Smith DK, Chillag K, Tibe, K. Adolescent participation in microbicide trials: a view from Botswana. Presented at: The International Consultation on Ethical Issues in the Clinical Testing of Microbicides, October 23–24, 2003; Warrenton, Virginia.

be enrolled in a special adolescent-only arm of a Phase 3 trial or enrolled along with women over 18 in a traditional, two-arm Phase 3 trial. The problem is that integrating adolescents into an overall Phase 3 trial would probably not yield sufficient data on young adolescents to assess effectiveness in adolescents as a category, because the number of participants would still be too small for statistically significant conclusions.

Ultimately, a full Phase 3 trial among younger adolescents will likely be necessary because the effectiveness of microbicides, unlike vaccines, may be affected by the immunological environment and cervical ectopy common in younger girls. Moreover, the protection achieved with microbicides is very likely to be affected by age-related behavior. Participants recommended further exploration of this issue.

7. Defining "Benefits" and "Standard of Care"

Among the thorniest ethical issues in clinical research on microbicides is the question: Which benefits should be provided—to whom and for how long? The challenge is, first, to define what is meant by "benefits" and then to properly balance these benefits against the risks and burdens of research.

The problem, in part, is that ethical discourse on appropriate benefits often refers to different things. Benefits can refer to the package of interventions offered to those in the trial's control arm or to the health services offered to all trial participants during the research (referred to as the trial's "standard of care"). The discourse on benefits can be further extended to include advantages offered to the wider community hosting the trial. Some benefits are tangible and immediate, such as access to improved health care; others may not materialize until far into the future (access to antiretroviral therapy (ART) if one becomes infected during an HIV prevention trial).

In terms of *material* benefits, no one disagrees that participants in a clinical trial should be reimbursed for costs such as transportation, time, and childcare; that they be given food while at the clinic; and that it is appropriate for them to receive gifts, such as T-shirts and tote bags, to mark milestones in the trial. It is also widely accepted that sponsors and investigators are obligated to provide medical care necessary to implement the research protocol in ways that are safe and scientifically valid.

Controversy begins to creep in when discussing medical or social service benefits beyond those required to conduct the trial, or providing benefits to trial participants that would not otherwise be locally available. Some argue that benefits beyond compensation for time and effort constitute "undue inducements" and are thus ethically problematic. Participants may be motivated to join the trial for access to an experimental treatment that they need, or in hope of continuing access if an experimental product is shown to be effective. Similarly, they may be motivated by a desire for better ongoing health care than is otherwise available locally, or simply by cash. Some prospective participants may want to participate—or may be pressured to participate—so that their communities receive collective benefits, such as improvements to the local health care infrastructure.

Others argue that inducements, even relatively strong ones, are not necessarily problematic. Motivations such as altruism, curiosity, and the desire for access to quality care are neither a priori "wrong" nor morally problematic. Problems arise only when inducements become coercive—that is, they edge toward "offers that cannot be refused." They become ethically problematic when they are so appealing as to impair proper judgment and cause a participant to ignore

or discount obvious risks. If people are implicitly pushed to do something that they would not do otherwise, the voluntary nature of participation is compromised, and inducements can be said to be "undue."

Clinical research protocols must be approved by regulatory authorities and ethics committees who examine risk-benefit ratios to determine whether it would be against the interests of "reasonable persons" to participate. While the weighing of risks and benefits is subjective, this approval process works to ensure that the balance between risks and benefits does not tilt too far in one direction or the other.

The general worry over inducements may thus be overstated. An issue of greater concern may be distributive justice. Is it appropriate to provide benefits to trial participants that are not available to others? Does the provision of exceptional health care services to trial participants—but not to other members of their families or communities—breed discontent or exacerbate local inequities? If ART is provided only to those who seroconvert during the trial—but not to all who are found to be HIV-positive at screening—is the principle of justice violated?

After grappling for two days with these questions, participants in the Consultation generally agreed upon three conclusions.

1. Researchers do have a special obligation to the participants in their trials, and possibly to their communities. This obligation derives from the notion of reciprocal justice.[1] Participants give more of themselves; and thus, they qualify for special treatment.

2. Researchers are not solely responsible for meeting health care related needs of trial participants. The researchers' obligation is to ensure that those who are screened or enrolled in trials have access to adequate health care, though not necessarily to provide it themselves.

3. Researchers should always try to reduce, not exacerbate, inequities. Nonetheless, disparities realistically exist everywhere in the world. To try to improve life for some—even if not for everyone—is not morally wrong.

Standard of care within trials: the debates

Consultation participants agreed that investigators (and their sponsors) ask a great deal of trial participants and therefore take on a special responsibility to them. Researchers have access to resources; they should use the opportunity of research to reduce suffering. In this view, the researchers' obligations to the larger society do not trump their responsibilities to individual participants. To sacrifice the interests of trial participants in the name of science or for long-term social benefit is not ethically justifiable, even more so because these "benefits" are uncertain and may not materialize.

Yet specific questions persist:

- What is the appropriate standard of care or prevention package within the trial?
- What are the researchers' obligations to those who seroconvert during the trial?
- What obligations are assumed for women who are recruited but screened ineligible for the trial—and how can these

[1] Reciprocal justice is a concept from ethics that says that someone who has benefited from the investment and sacrifice of others owes them proportional recompense.

obligations be met? (The number of women who are HIV-positive at screening may be significantly greater than the number who seroconvert during the trial.)

- What are researchers' obligations to local communities? To the host country?

The concept *standard of care* is rooted in the physician's fundamental ethical obligation to provide patients with the best possible care. It marks the boundary between expected standards of practice and medical negligence.

Over the past decade, the concept of standard of care has migrated into the general discourse of research ethics. In the context of clinical trials, it generally refers to one of two things: the general package of health services offered to individuals who participate in trials, or more specifically, the treatment or care provided to members of the control arm of a trial. In recent debates over placebo-controlled trials, the term has most frequently been used to refer to the treatment or care that should be offered to members of the control arm.

The debate in the clinical research, however, is over *which* standard of "best care" should be provided in the context of a trial. Is it the "best proven" treatment or intervention available globally (sometimes referred to as the "universal standard"[2])? Is it the best care that is available locally (or at least should be, according to national health standards)? Or is it something in between?

In addressing this problem, most individuals agree that accepting local health-care realities—if these realities are grossly inadequate—does not constitute a sufficient standard for ethical research. Yet how far beyond the local standard can or should investigators be expected to go? Is it acceptable to design studies to a standard that represents the highest level of care that could be sustained locally? Or, does justice imply that every person enrolled in a clinical trial—regardless of the local circumstances at the trial site—receive the same best-proven treatment that would be received if the trial were to take place in an industrial country?

An argument against requiring participants in the control arm to receive the best-proven intervention available globally is the need to answer a scientific question relevant to the host community. If community members participating in the control arm of the study receive a standard of care that cannot be sustained locally, the trial may not yield valid comparative data to assess the effectiveness of the experimental intervention. Those who take this position argue that many revolutionary public health interventions, including oral rehydration for childhood diarrhea, would never have been proven effective if effectiveness trials had been forced to compare this "low-tech" intervention against hospital-based, intravenous rehydration, which was the standard of care for severe cases of diarrhea in the industrial world.

Others argue this question in purely pragmatic terms. Whether or not it would be desirable for them to do so, researchers conducting clinical trials simply do not have the capacity to fully redress global disparities in health care. For better or

[2] The Nuffield Research Council, which introduced the term into research ethics, defines "universal standard of care" as "the best current method of treatment available anywhere in the world for a particular disease or condition." Others prefer "highest standard of care" in referring to the same concept.

worse, that responsibility lies with policymakers, governments, and donors. The role of the researcher is to advance knowledge with potential long-term benefits for a great many people, not provide short-term benefits to a small population who happen to be in a trial.

Those who favor providing the best-known intervention as the ethical standard argue that to do otherwise constitutes a fundamentally unjust double-standard and that participants not receiving the best-known interventions could suffer from preventable harm. Also, it can be argued that international research initiatives *are* legitimate vehicles through which global inequalities in access to health care can be reduced. Conforming to a universal standard also avoids inconsistencies in the care provided among different sites in a multicountry study. To achieve the necessary numbers, trials frequently enroll participants in many countries and sites and then pool the data for analysis. If all decisions are negotiated locally based on local realities, different people in the same trial could receive different levels of care.

The ethical basis for extending benefits to communities, rather than to trial participants, is less obvious. There is a certain amount of controversy on this matter, especially between research sponsors and the communities that participate in research. Ethics is, however, not the only grounds from which to argue this point. Both communities and countries should carefully consider how best to negotiate the benefits to be received through participation.

International guidance on standard of care

International guidance documents are inconsistent in their positions on standard of care and appropriate use of placebos. The most frequently cited document, the Declaration of Helsinki, contends that the best-known methods of treatment, diagnosis, and prevention should be provided. Paragraph 29 states:

> *The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.*

Yet an exception may be made under certain circumstances. In November 2001, the World Medical Association (WMA) clarified Paragraph 29 as follows:

> *The* WMA *hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:*
>
> *Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method.*[3]

[3] "World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects," Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended most recently by the 52nd WMA General Assembly, Edinburgh, Scotland, 2000. This is an amendment in the form of a footnote to Paragraph 29, approved by the WMA General Assembly, Washington DC, 2002.

Paragraph 29 of the Declaration of Helsinki has been widely interpreted to mean that participants in the control arm of a trial are entitled to a "universal" standard of care.

Other international guidance documents differ. Box 5 summarizes the positions of key guidelines on the provision of health care to participants in clinical trials. Box 6 summarizes guidelines on the use of placebos in clinical research. With the exception of the Declaration of Helsinki, no other document requires investigators to provide participants with the best standard of care available anywhere. Clearly, opinion is still widely divided on what ethics requires of clinical research. In terms of standard of care, debate is active, unresolved, and highly contentious.[4,5]

To the extent possible, scientific rigor and benefits to study participants should not be viewed as mutually exclusive. Both can be addressed in several ways. One part of the

BOX 5: Guidelines on Required Provision of Health Care for Participants in Clinical Trials

Declaration of Helsinki

- No specific mention of HIV prevention trials.
- No specific obligations regarding provision of medical care during research.
- General statement of obligation, open to strong and weak interpretations (Paragraph 10: "It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.")

CIOMS International Guidelines

- Guideline 21: Ethical obligation of external sponsors is to provide health-care related services.
- Must provide health-care services that are essential to the safe conduct of the research.
- External sponsors are ethically obliged to ensure the availability of treatment for subjects who suffer injury as a consequence of research interventions.

UNAIDS Vaccine Guidance Document

- Guidance Point 16: "Care and treatment for HIV/AIDS… should be provided to participants, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host county in light of [circumstanced specified]."

Nuffield Council on Bioethics

- Endorses Guidance Point 16 of UNAIDS Vaccine Guidance Document.
- "We conclude that where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered is the best available intervention as part of the national public health system for that disease."
- Agreement should be reached before research begins about the standard of care to be provided to subjects.
- Any proposal for care of a lower standard must be justified to the relevant research ethics committees.

answer is close consultation with the communities involved, empowering them with tools and information to analyze and prioritize choices. Moreover, improving local standards of care may enhance the quality of research results by increasing trust and encouraging sustained participation in the trial.

Standard of care within trials: the reality

In the real versus the ideal world, determining the standard of care within trials depends on many factors—for starters, the size and budget of the trial and the availability of support from government, communities, nongovernmental organizations (NGOs), and local providers. Research projects may not be able to compensate fully for the inadequacies in local health care systems. Nevertheless, there is much that investigators *can* do: They can train health personnel, bring in new equipment, standardize care across sites, and raise awareness for services not locally available. They can assist local services to address the increased demand when previously undiagnosed health problems are identified. They should be in dialogue with the local authorities and providers, and they can make clear, up-front arrangements on the provision of services during the study. Similarly, they can support community advocacy to demand that the government improve and expand the provision of services.

In reality, the concept of a universal "fixed" standard can be problematic. Contexts vary, and something that may be feasible or optimal in one place may be inappropriate or undoable in another. Furthermore, the "state of the art" constantly changes. The expected standard of care may no longer be right by the time the trial has been underway for some time.

Participants endorsed the view that sponsors should improve the local standard of care available during the conduct of research trials. The goal should be to move toward state-of-the-art care in the long run while doing as much as possible in the meantime. South African ethicist Solomon Benatar first advanced this notion, which he referred to as "ratcheting up" the standard of care. As Shapiro and Benatar observe:

> *[Standard of Care] should include several interlinking features that would promote fairer distribution of burdens and benefits in both short and long term for participants in communities. First, research should be undertaken in the best interests of trial participants by involving them in decisions around research design and implementation. Second, the dignity of participants should be respected, wherever they are in the world. Third, consideration should be given to the broader community benefit that could be achieved by raising the standard of health care through partnerships created by the research endeavor. That the ideal of first world health care cannot be achieved immediately in developing countries should not be a deterrent to efforts to raise existing levels of care. By setting high ideals and working towards, them, the standard of care could be progressively ratcheted upwards.* [6]

[4] Lie RK, Emanuel E, Grady C, Wendler D. The standard of care debate: the Declaration of Helsinki versus the international consensus opinion. *Journal of Medical Ethics*. 2004; 30:190–193.

[5] Schüklenk U. The standard of care debate: against the myth of an "international consensus opinion". *Journal of Medical Ethics* 2004;30:194–197.

[6] Shapiro K, and Benatar SR. HIV Prevention Research and Global Inequality: Steps Towards Improved Standards of Care. *Journal of Medical Ethics*. 2005;31:39–47.

BOX 6: Guidance Related to Use of Placebos in Clinical Trials

Declaration of Helsinki

- Paragraph 29: "The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods."

CIOMS International Guidelines

- Guideline 11: "As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or no treatment."
- A placebo may be used (i) when there is no established effective intervention; (ii) when withholding an established effective intervention would expose the subjects to, at most, temporary discomfort or delay in relief of symptoms; (iii) when use of an established effective intervention as comparator would not yield scientifically reliable results and use of a placebo would not add any risk of serious or irreversible harm to the subjects.
- Commentary of Guideline 11: "An exception to the general rule is applicable in some studies designed to develop a therapeutic, preventive, or diagnostic intervention for use in a country or community in which an established effective intervention is not available and unlikely in the foreseeable future to become available, usually for economic or logistic reasons. The purpose of such a study is to make available to the population of the country or community an effective alternative to an established effective intervention that is locally unavailable."

Nuffield Council

- Wherever appropriate, participants in the control group should be offered a universal standard of care for the disease being studied. Where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered to the control group is the best intervention available for that disease as part of the public health system.

Council of Europe

- Article 23.2: "Research shall not deprive participants of necessary procedures… In research associated with prevention, diagnosis, or treatment, participants assigned to control groups shall be assured of proven methods of prevention, diagnosis or treatment."
- "It is expected that a proven method of treatment that is available in the country or region concerned be utilized."

National Bioethics Advisory Commission Report

- Researchers and sponsors should design clinical trials that provide members of any control group with an established effective treatment, whether or not such treatment is available in the host country. Any study that would not provide the control group with an established effective treatment should include a justification for using an alternative design. Ethics review committees must assess the justification provided, including the risks to participants, and the overall ethical acceptability of the research design.

European Group on Ethics in Science and New Technologies

- Opinion #17: The use of placebos should be regulated in developing countries in principle by the same rules as in European countries. Any exception must be justified: an obvious one is when the primary goal of the clinical trial is to try to simplify or to decrease the costs of treatment for countries where the standard treatment is not available for logistic reasons or inaccessible because of cost. It may thus be justified to derogate from the rule of best-proven treatment. The justification of using a placebo must be clearly demonstrated in the research protocol submitted to the ethical committees and especially approved by the local committee.
- It should be noted that two members of the group recorded their consent, noting "Use of a placebo to develop a low cost treatment could mean accepting a 'double standard' for rich and poor countries."

UNAIDS Guidance for Preventive HIV Vaccines

- Participants in the control arm of a future Phase 3 HIV preventive vaccine trial should receive an HIV vaccine known to be safe and effective when such is available, unless there are compelling scientific reasons which justify the use of a placebo.

In short, establishing appropriate standards of care is a process. Research endeavors should leave participants and their communities better off after the trial, not merely "not worse off." To achieve this goal requires persistence, creativity, and the capacity to act in partnerships.

From principles to protocol

Even when there is a consensus that care should be improved, actually making and incorporating health care decisions into a trial protocol is still difficult.

Investigators face hundreds of concrete decisions about individual aspects of care: Should contraceptives be provided directly by the trial or can participants get adequate care from local family planning clinics? What if a pelvic exam indicates that a woman has cervical cancer and no local treatment is available? Should viral load and CD4 tests be done for women who are HIV positive at screening?

The ethics document of the HIV Prevention Trials Network (HPTN)[7] suggests that investigators categorize three groups of care: first, the services offered to participants to help them remain HIV negative (that is, the prevention package); second, the services integral to the conduct of the trial (for example, HIV and pregnancy testing); and third, health or other benefits beyond those required to evaluate the study endpoint.

Study teams should next consider the pros and cons of particular elements of care in each of these three categories. They need to consider the possibility of alleviating suffering (narrowly or broadly), reducing (or exacerbating) inequities, creating ethical inducements (or unfair pressure) to participate, and contributing to (or undermining) the sustainability of care. Researchers can analyze these elements in consultation with key stakeholders and community members. Together, they should work to define and decide upon the

[7] See Chapter 3, Table 4 for a summary of key guidance documents.

appropriate package of care. This includes consideration of unintended consequences and ways to sustain or reduce the negative impact of care ceasing at the trial's end. Some real-life challenges faced by investigators in HIV prevention trials are explored in Box 7.

Participants agreed that services provided within the study—at the very least—should be better than the local standard of care. If the "best proven" standard of care is not to be provided, the rationale should be set forth in writing, with neither expediency nor expense alone constituting adequate justification.

The practical advantages of providing improved care to the entire community—not just to those enrolled in the study—were also recognized. This reduces reinfection rates and promotes sharing of benefits, for example, through improved STD treatment. It also avoids concerns about generating undue inducement to enroll. One suggestion was to aim for a sustainable standard of care for the whole community that is as good as or better than that defined by government health policy. Where such policies exist, they often dictate standards of care that are better than what is available locally, thus reinforcing the importance of implementing policies and

BOX 7: Challenges in Standard of Care: A Survey by the HIV Prevention Trials Network

In 2003, the HIV Prevention Trials Network (HPTN) carried out an email survey of standard of care at ten trial sites. The purpose was to learn about care currently provided, care available at the same facilities but outside the research, and care accessible through referrals.

In general, the services available to the general population (either free or for a fee) were found to be more limited than those available to research participants. The trial participants received fairly comprehensive HIV prevention services, including voluntary counseling and testing (VCT), as well as male condom distribution and counseling. Antiretroviral treatment (ART) was not offered in the trial benefits package at the ten sites surveyed. However, ART was available in the same facilities at a subsidized cost in three of the locales. At three sites, trial participants were offered treatment of opportunistic infections. Four sites provided two-dose nevirapine to pregnant women for prevention of mother-to-child transmission. However, no sites offered breast milk substitutes, and only two made referrals for substitutes.

In general, reproductive health services offered to trial participants tended to be minimal or nonexistent, though all women in microbicide trials could arguably benefit from access to family planning or obstetrical services as part of study follow-up, regardless of their HIV status.

Three of the nine sites also provided female condoms to participants. This raises a new question, illustrating the difficulties in establishing standards for research participants' care. Among experts, interpretations differ on the evidence base for the effectiveness of female condoms. So, should female condoms be included as part of a standard prevention package?

The HPTN assessment serves as a reminder of the challenges that researchers face in attempting to ensure appropriate standards of care for women in microbicide trials. The results helped HPTN to identify areas where referrals needed to be strengthened and other steps to improve access to care and treatment for planned microbicide trials. It should be noted that access to HIV treatment and care has improved significantly at some sites since the survey was completed as a result of global efforts to scale up treatment access.

programs to the public health system. Together with local officials, researchers should advocate that governments sustain these services when the trial ends.

Still unresolved is the question of whether higher standards should be set for international research sponsored by outside parties, versus locally initiated research. Requiring the "best proven" standard of care for all research studies could dramatically undermine the capacity of local investigators to pursue relevant research. The question is whether a local investigator, who may not have the means to provide the best proven treatment, can nonetheless proceed while still expecting industry-sponsored researchers to provide "best proven" treatment in their trials. A number of participants argued that while standard of care for locally initiated, low-budget research could be lessened, international and pharmaceutically sponsored research should be held to the highest possible standards, lest flexibility be interpreted to mean that anything better than local care is appropriate, even by those with the resources to provide more.

Microbicides, placebos, and the investigator's dilemma

All ongoing microbicide trials provide free access to condoms and state-of-the-art counseling on risk reduction. They also provide STD testing and treatment (some treat only symptomatic STDs whereas others routinely screen for STDs using high-end diagnostics). These interventions are known to reduce HIV transmission; so current vaccine and microbicide trials do *not* have a classic "no-treatment arm." They do, however, use placebos for "blinding" purposes, that is, to keep both participants and research staff from knowing which group received the active microbicide.

Significantly, both the microbicide and vaccine fields have rejected classic placebo-controlled trials. Although the quickest and most "efficient" microbicide trial would theoretically be to compare a candidate microbicide with a placebo microbicide without offering condoms and STD treatment, this scenario has been widely rejected as unethical.

Evidence demonstrates, however, that even with access to condoms and extensive risk-reduction counseling, women nonetheless experience significant rates of HIV infection, even those who are enrolled in prevention trials.[8] It is precisely the fact that many women cannot use condoms that makes the search for a new prevention tool so urgent. The consequence of this reality is that microbicide studies *are* able to evaluate the effectiveness of candidate products, even though condoms are available and actively encouraged, and STD treatment is provided.

That said, reducing the incidence of HIV infection in a study population does diminish the statistical power of the study in the sense that it becomes more difficult to demonstrate the efficacy of a microbicide. Therefore, researchers may have—or at least be perceived to have—a disincentive to rigorously promote the use of condoms and other risk-reduction interventions. This so-called investigator's dilemma has long been acknowledged and extensively discussed within the microbicide community.[9] Most study nurses, counselors, and staff are fully committed to the health and well-being of

[8] Bartholow B, Buchbinder S, Celem C, et. al. HIV risk behavior over 36 months of follow up in the world's first HIV vaccine efficacy trial. *Journal of Acquired Immune Deficiency Syndrome*. 2005; 39(1): 90–101.

[9] DeZoysa I, Elias C, Bentley M. Ethical challenges in efficacy trials of vaginal microbicides for HIV Prevention. *American Journal of Public Health*. 1997; 88(4):571–575.

participants during the trial. They understand their clear responsibility to help participants reduce their HIV risk. However, to minimize both real and perceived conflict of interest, participants in the 1997 ethics consultation recommended that investigators consider enlisting a separate entity to conduct the trial's risk-reduction counseling. This practice helps to address concerns that the rights of participants could conflict with research goals.

Yet similar questions remain. What if interventions other than condoms and STD treatment are shown to reduce risk—for example, male circumcision, herpes treatment, or a novel microbicide? Should these interventions become part of the mandatory package of prevention services offered to participants in HIV prevention trials? Should experimental interventions be included in the standard of care in future prevention trials, even if not fully accepted as standard practice in HIV prevention programs? These questions are explored in greater depth in Chapter 9, "Testing Second-Generation Microbicides."

8. Antiretroviral Treatment in Clinical Trials

HIV treatment in prevention trials

Reflecting a marked change from the past, provision of antiretroviral treatment (ART) has moved to the forefront of current debates on the ethics of HIV prevention trials. In the 1997 ethics symposium, discussion of ART was not even on the agenda, because ART was then considered too complicated and expensive for resource-poor countries. In recent years, however, antiretroviral drugs have improved and costs have significantly dropped. Treatment activism has increased, so the issue is widely being reexamined.

UNAIDS originally spearheaded the discussion on provision of ART, especially as it relates to those who seroconvert during vaccine trials. Between 1998 and 2001, UNAIDS organized regional consultations to discuss HIV treatment in the context of vaccine trials in Brazil, Thailand, and Uganda. However, delegates could not reach consensus on whether vaccine trials—as a matter of ethics—should guarantee access to ART to trial participants.

The UNAIDS Brazil consultation concluded that participants should receive the level of HIV treatment available in the country sponsoring the trial. This would mean ART for at least the duration of a trial, and longer if that could be negotiated. Delegates to the Thai meeting argued for a level to be decided upon by the host country. This would include monitoring, prevention, and treatment of opportunistic infections, and palliative care—though not necessarily ART. Whatever was to be provided should be made reasonably available for the lifetime of the participants. The Ugandan consultation concluded that the local standard of care should be respected. It found no imperative to provide a level of care consistent with that of the sponsoring country or with the highest level of care available in the world.

In 2000, UNAIDS declared, "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."[1]

The pros of ART in the benefits package

Throughout these discussions, arguments have been made for and against making ART obligatory in the benefits package. The following arguments are in favor:

- Sponsors have an ethical obligation to offer the best care according to their resources.
- Participants in sponsor and host countries should receive equal care, not a double standard.

[1] UNAIDS. *Ethical Considerations in* HIV *Preventive Vaccine Research*. UNAIDS Guidance Document. Geneva: UNAIDS; 2004.

- Participants in the research deserve to receive the highest possible standard of care in light of the risks and burdens that they assume.
- Some participants might engage in risky behavior because of a common misconception—that the product provided during the trial guarantees protection. (This is referred to as the "therapeutic misconception."[2])

The cons of ART in the benefits package

These arguments have been made against the obligatory provision of ART:

- Promising ART might create an undue inducement to individuals who see themselves at risk but do not otherwise have access to treatment.
- Giving ART to trial participants might exacerbate local inequalities and create problems within families or communities.
- Most women involved in prevention trials are uninfected, so ART is not relevant to them. Providing other kinds of health services would be more beneficial to a much larger number of women.
- Host countries and communities have the sovereign right to determine the balance of risks and benefits that they are willing to accept. Furthermore, they should be able to ascertain which services they believe to be of maximum benefit and thus want included in their package.
- Governments might dodge commitments and responsibility to provide long-term care and ART treatment, especially if they believe the research sponsors will provide it.
- Exclusive focus on ART may divert attention and resources from less-studied aspects of HIV treatment and care that potentially affect greater numbers of people.
- If they have to assume a substantial additional expense because of obligatory ART, prospective sponsor governments might be disinclined to finance trials.

ART in the context of microbicide and vaccine trials

As the provision of ART has come within reach, those involved in HIV prevention trials are rethinking how ART should and will affect their research. Recent consultations have brought together a diverse spectrum of stakeholders to debate and develop coherent policies regarding access to HIV treatment in the context of prevention trials.[3]

Several vaccine networks and sponsors—including the HIV Vaccine Trials Network (HVTN), the South African AIDS Vaccine Initiative (SAAVI), and the International AIDS Vaccine Initiative (IAVI)—have committed to

[2] "Therapeutic misconception" is an ethical term that refers to a tendency among trial participants to wrongly assume that participation in the trial will necessarily benefit them personally. It frequently arises because people do not fully understand the difference between health care provision (where the patient can rightly assume that whatever is given is believed to work) and research (where clinicians are attempting to figure out if a new intervention will work). In prevention trials, the therapeutic misconception refers to people believing that the new product protects them, even though they have been counseled that the experimental product is unproven and that they may be receiving a placebo.

[3] The recent consultations include: the South African AIDS Vaccine Initiative (SAAVI) meetings in December 2001 and August 2002, the South African Microbicides Research Institute (SMRI) meeting December 2002, Global Campaign for Microbicides/ International AIDS Vaccine Initiative (IAVI) meeting in February 2003, the South African National Consultation in April 2003, and the WHO/UNAIDS meeting in July 2003.

providing ART to those who become infected during vaccine trials. In the words of SAAVI, "The question is not if, but how."

In the case of vaccines, the rationale for ART is scientific as well as ethical. Participants in vaccine trials need to be followed for several years to determine whether a vaccine that does not prevent infection nonetheless reduces the time to the viral set point or to disease. Over this extended period, the CD4 count of many individuals may deteriorate, and they may become symptomatic. Thus, participants may still be enrolled in vaccine trials when they become eligible for HIV treatment under WHO guidelines.

A question still being debated is *who* is responsible for providing the treatment—research sponsors, the host nation, or the sponsoring governments. A number of approaches to long-term treatment are being explored, including creation of treatment funds and insurance schemes. In 2004, IAVI held in-country consultations, first in Uganda and India, to develop plans for HIV treatment access. Their goals are to collaborate with those working on treatment—to prioritize vaccine research sites in ART scale-up efforts—and to explore joint ventures to create access to vaccines and treatment.

In July 2003, WHO/UNAIDS convened a consultation, HIV Treatment for Intercurrent Infections. This brought the vaccine and microbicide worlds together, along with social scientists, ethicists, community representatives, and donors. Together, they affirmed that providing ART conforms to several fundamental ethical principles: *beneficence*, by which researchers are obliged to maximize benefits to participants; *reciprocity*, which suggests that those who contribute important data to the study by becoming infected deserve something in return; and *justice*, by which participants in trials who seroconvert should be treated equally, regardless of their setting.

The WHO/UNAIDS consultation produced the following recommendations:[4]

- Trial participants who seroconvert during HIV prevention trials should have access to quality treatment and care, including ART.
- Before a trial starts, agreements should be reached among all the stakeholders on the level of care and approaches to treatment. This includes sponsors, researchers, communities, host governments, and industry.
- Funding mechanisms that will ensure continued treatment and care should be fully discussed and agreed on by the participating organizations.
- The trials should contribute to building local capacity, so that treatment and care can be accessed through local health and social services.
- Where the local health system is unable to provide adequate services, alternative mechanisms—for example, earmarking of funds for services—must be put in place.
- Although institutions like the World Bank and the Global Fund to Fight AIDS, Tuberculosis, and Malaria (The Global Fund) do not finance basic research and clinical trials directly, they could nevertheless provide resources that help facilitate research, such as infrastructure, as well as treatment and care.

[4] WHO/UNAIDS. Treating People with Intercurrent Infection in HIV Prevention Trials: Report of a WHO/UNAIDS Consultation. *AIDS.* 2004;18(15):W1-W12.

- Research participants, partners, and family members found to be HIV positive at the time of screening should be referred to local facilities for treatment. If local facilities are not adequate, special arrangements should provide treatment and care.

Even though the balance of opinion is shifting toward provision of ART in the context of prevention research, persistent questions remain unanswered. Who should receive ART—trial participants only, those screened out, family members, or trial staff (sometimes infected with HIV)? Who should be responsible for providing and paying for the ART treatment—and for how long?

In general, most networks and organizations that intend to provide ART for those who seroconvert during a trial are not planning to provide ART for family members, nor for prospective participants who were screened out because they are HIV positive.

When to initiate ART? Many researchers look to WHO guidelines, which recommend that physicians initiate therapy when a patient's CD4 count declines to less than 200 cells per cubic millimeter, or when clinical signs of AIDS become apparent. For those who seroconvert during microbicide trials, ART may not be required until many years after the trial officially ends. This implies a promise that may be easier to make than to keep. For the commitment to be meaningful, researchers must set up sustainable follow-through mechanisms. This means capacity to track, deliver, pay for, monitor, and continue ART for many years after the trials end for a relatively small number of people who may be geographically dispersed.

It should be remembered that most women involved in prevention trials are not infected. Some Consultation participants expressed concern that by focusing too narrowly on ART, donors and advocates may loose sight of the reproductive health care needs of the majority; moreover HIV positive women typically have a plethora of unfulfilled needs beyond access to drugs. A recent survey of services available at HPTN-related trial sites revealed that many lack access to even basic services, such as contraception and nutritional support, prophylaxis, and treatment for other common AIDS-related ailments (see Chapter 7, Box 7).

Other participants in the Consultation countered that ART access has been among the weakest links in AIDS care in developing countries and, as such, warrants special emphasis in discussions of the ethics of clinical trials. Most participants agreed, however, that far more could be done to provide a range of services to women who become infected. This includes reproductive health care, nutrition assistance, treatment of symptoms, and the prevention of opportunistic infections and cancers.[5] A "mapping" of what is and is not included in trial-site benefits packages was suggested as a highly useful next step.

Community consultation

Throughout the discussion, a unifying refrain was to confer with participant populations and communities hosting the research. The benefits package should be determined through a transparent decision-making

[5] One speaker noted, for example, that women are often most bothered by the itchy and unsightly rash and express a desire for treatment for their skin.

BOX 8: A South African Perspective on the ART Debate

Cathy Slack, an ethicist from the University of Kwazulu-Natal, provided a South African perspective on researchers' and trial sponsors' ethical obligation to provide ART to trial participants who seroconvert during prevention trials.[1] The analysis was developed by the HIV/AIDS Vaccine Ethics Group (HAVEG), a working group of the South African AIDS Vaccine Initiative (SAAVI).

Two main arguments have been advanced to support the idea that researchers are ethically obliged to provide ART to participants—first, as compensation for research-related harms, and second, as fair distribution of risks and benefits and reducing inequalities.

Compensation for research-related harms. Although agreeing with the principle that individuals deserve compensation for trial-related injuries, HAVEG argues that this applies only if the test product or the trial itself causes the infection. In microbicide trials, participants become HIV infected *despite* trial-related interventions, not because of them. Others have countered that participation in an HIV prevention trial may cause some people—who mistakenly believe that the candidate product will protect them—to increase their risky behavior; and for this reason, HIV infection during the trial could be viewed as "research related." This position maintains that "behavioral disinhibition" because of the "therapeutic misconception" could be considered a research-related harm.

HAVEG reviewed studies on participants' understanding of the information received about vaccines and their expectations of its effectiveness. They concluded that it is possible, albeit a challenge, to provide participants with a good understanding of the experimental nature of the vaccine, including the fact that it may not offer protection. They also examined the empirical evidence of how risk behavior changes during vaccine and microbicide trials, concluding that risk behavior does not generally increase and is indeed more likely to decline as the trial progresses. Moreover, increase in risky behavior cannot easily be attributed to the trial as distinct from a myriad of other possible causes. While this argument may have some merit at the individual level, HAVEG concluded that it would be hard to justify a "general obligation" for sponsors to provide ART based on the principle of compensation for harm related to the research.

Fair distribution of risks and benefits and reducing inequalities. While providing ART to those who seroconvert would reduce inequalities between industrial and developing countries, providing comprehensive treatment to the few people who seroconvert is not necessarily the best way to redress global health care injustices. One could convincingly argue that this goal would be better served by improving basic health care infrastructure in trial communities. Likewise, providing ART might exacerbate or potentially introduce local inequities—for example, between the people who are already HIV positive at the time of screening and those who seroconvert during the trial, or between those enrolled and their partners or children who may also be HIV positive. (That said, HAVEG also acknowledged that it would be impossible to do any kind of development work without introducing some local inequalities.)

Finally, might the offer of long-term ART be construed as an "undue inducement," motivating prospective participants to take on risks and burdens that they would otherwise reject in order to ensure future access to ART? While acknowledging that some participants might calculate this future benefit as part of a rational decision process, the benefit is uncertain and probably assumes too many steps to

Box 8 Continued on next page

BOX 8: A South African Perspective on the ART Debate *(Continued)*

strongly distort the immediate risk-benefit calculation. On balance, they cautioned against classifying provision of ART as an "undue inducement."

According to HAVEG, these two arguments in themselves do not make the case that sponsors and investigators are obligated to provide ART to infected individuals. However, justice-based arguments do exhort sponsor-investigators to reduce inequalities, despite differences in interpretation of the most "fair" arrangement—for example, whether to aim for comprehensive treatment for a few, or community-level improvements for the many? Wherever researchers and their sponsors have it in their power to reduce suffering of participants in their trials, they should do so to the utmost on the grounds of positive beneficence.

[1] For a more detailed accounting of these arguments, see: Slack C,. et al. Provision of HIV treatment in HIV preventive vaccine trials: a developing country perspective. *Social Science and Medicine*. 2005; 60:1197–1208.

process, not only *involving* the community but prioritizing their expressed wishes. This process understands and accepts that communities do not always express the priorities that researchers and advocates expect.

How a benefits package is viewed and constructed, for example, depends very much on where one happens to be sitting. In the global South, deciding which benefits to include is a process of deciding upon best allocation of scarce resources among many equally valid and compelling needs. For example, HPTN focus group research on health-related priorities found that although women were concerned about diseases such as HIV, they were just as concerned about inadequate hygiene, poor nutrition, and the lack of transportation to obtain care. Other priority needs included lack of staff, drug shortages, and the need to improve the quality of treatment at health services.

In a focus group with HIV positive women, HPTN elicited comments on hypothetical treatment scenarios. The first was that HIV positive women in the trial and their families would be referred for treatment services. The second was that all women in the trial would receive "basic" health care services and HIV positive women and their families would be referred for treatment. The third was "best care," including ART for HIV positive women until the end of the trial and referrals after the conclusion of the trial. Among these choices, the women found the third option most "unfair," because they distrusted long-term promises and rejected the notion of women receiving treatment not available to their partners and families.

Community involvement entails other challenges. If the benefits package is to be developed in consultation with the community, how do researchers figure out who speaks for the community? How do they handle the inequalities between research sponsors and hosts, which may cause a "race to the bottom" in which the urgency of a community's needs causes it to accept research that appears to offer *any* benefit? If the broader community plays a major role in determining the benefits

package, researchers need to take care that participants who are marginalized within those communities are not exploited. When individual and community interests diverge, they must be fairly reconciled.

Even if investigators are able to reach agreement with the trial site communities on what the benefits package should include, many researchers still face formidable bureaucratic hurdles from their donors. For example, as a matter of policy, the US National Institutes of Health (NIH) prohibits the use of clinical research funds after the conclusion of a trial. Without access to funding, researchers can do little to make good on promises to provide services after a trial ends. Thus, advocacy to change donor policy must also be taken on as a high priority.

Clearly, an ad hoc approach to clinical trials is unlikely to work in the face of such complexities. Before the research starts, a well-structured plan must be developed that involves the full gamut of actors and takes the local context into account. Partners are needed who can contribute to solutions. This means investing in local institutions to help create implementation mechanisms for plans such as continuing care when the clinical trials end.

At the very least, researchers should take advantage of existing opportunities to cooperate with ART expansion efforts, such as those being rolled out by the Global Fund and the United States government. Another option is to explore enrolling microbicide trial participants who are HIV positive into a parallel treatment trial. Researchers should work with existing care facilities and NGOs that provide care and treatment for infected individuals, and with networks of women living with HIV/AIDS. Specifically, they should actively seek to apply the GIPA standard (Greater Involvement of People Living with AIDS). Signed by 50 countries, the GIPA standard encourages groups to seek out and engage people living with HIV/AIDS. Finally, they should join the global movement for greater access to treatment.

Indeed, embedding microbicides research into human rights and sexual rights perspectives requires that researchers fight actively for all women's rights to dignity, respect, and well being. This requires advocacy to expand services to meet the diverse needs of women in the broader community—for example, services for unwanted pregnancy, violence, and STDs.

9. Testing Second-Generation Microbicides

Framing the terms for the next generation

As of early 2005, five microbicidal products were in or entering late-stage clinical trials (see Chapter 2, Table 2 and Table 3). Meanwhile, another two dozen products are in earlier stages of testing. As first generation products move through effectiveness trials and beyond, new questions arise. How effective must a product be to warrant regulatory approval and introduction? How to assess the long-term safety and effectiveness of products already licensed? Will access to an effective product be guaranteed to participants after a trial? What are the implications of identifying a weakly protective product for evaluating second- and third-generation microbicides?

For new products to be licensed, drug regulators—especially the US Food and Drug Administration (FDA)—usually require at least two randomized controlled trials or one "pivotal trial" that provides as much compelling evidence of effectiveness as two trials. If a single trial shows evidence of effectiveness but does not yet meet standards for FDA approval, some countries may nonetheless license the product. Others may require a second trial, as would the United States.

Under such circumstances, some countries may call for "bridging studies" to look at the safety and acceptability of a new product for specific populations. Bridging studies usually require hundreds of participants, about the same as a Phase 2 trial; and they typically involve 6 to18 months of follow-up. It is not clear whether a control arm should be used in a bridging study or whether everyone should receive the product. Another challenging question is what should be said about the effectiveness of the product during the informed consent process. Although the initial trial may have generated some information about effectiveness, it is unlikely to have yielded sufficient evidence to provide clear counseling messages on how effective the product would be if used consistently.

Repeating the trial to confirm effectiveness raises similar questions. Given evidence of weak effectiveness, is it ethical to conduct a second trial that compares the test product and condoms to an inactive gel (placebo) and condoms? Specifically, some have argued that once evidence of effectiveness is shown, it is not ethical to repeat the trial in another setting or to plan and implement a similarly designed study of a new candidate microbicide.

Consultation participants spent considerable time grappling with the implications of this question for the design of second-generation microbicide trials. For example, suppose that a current trial in the field yields evidence of effectiveness. Would the new product then have to be given to all participants in future trials as defined by the basic standard of care? If so, what are the

implications for trial size and for procedures? Similarly, suppose that a microbicide is found to be effective in a particular population. Can and should the trial be repeated elsewhere if there is reason to believe that conditions influencing its effectiveness may differ in other populations? The group concurred that complex problems such as these will require reflection and debate stretching well beyond the Consultation.

Applying the standard of care argument

There are at least two ways to consider the "next-generation" questions. First, the problem may be framed in terms of standard of care. When does a new prevention tool become part of the "standard prevention package" that must ethically be provided to all participants in HIV prevention trials? Is it reasonable to consider something to be "standard care" before it is widely available outside clinical trials? If condoms and STD treatment provide excellent HIV prevention when used consistently, is it ethically necessary to add new methods to the background package of prevention if this makes the task of evaluating novel (but potentially better) interventions impossibly complicated and costly?

As discussed earlier, some ethics guidance documents recommend that research participants in the control arm of a trial receive the "best current prophylactic, diagnostic, and therapeutic methods" (Helsinki Declaration). By contrast, others demand "an established effective intervention" (CIOMS and NBAC Report), or "a universal standard of care… or at a minimum the best intervention available for that disease as part of the public health system" (Nuffield Council).

The ethical principle of equipoise

The second approach to framing the next-generation question is in terms of the ethical principle of equipoise. The term *equipoise* describes a situation where genuine doubt exists on whether one product or intervention works better than another. To understand equipoise, imagine that someone needs to decide whether it is ethically permissible to enroll an individual in a clinical trial. Assume that the decision-maker consults with experts in the field about available methods, concluding that there is considerable uncertainty about which is better. Perhaps this uncertainty is because the vast majority of experts agree that there is reasonable doubt about which method is better; or perhaps they strongly disagree among themselves on which is best, which also translates to a high degree of uncertainty. With no reason to unequivocally choose one option over another, and no other available intervention that would be more attractive, then enrolling individuals into either the experimental or the control arms would be considered ethical, and the trial may proceed.

While equipoise appears to be a straightforward concept, it is not easy to put into practice. In its application, there is much room for interpretation. Who decides, for example, when enough is known to weigh the options? Is equipoise related to the population and can it differ in different settings? Furthermore, equipoise is a necessary but insufficient condition for ethical research. If equipoise were obtained under unjust or exploitative conditions, the research could still be considered unethical—for example, despite genuine uncertainty on whether one or another poison kills human beings more quickly, it would still be unethical to implement an experiment to resolve the issue.

Alex John London, an ethicist from Carnegie Mellon University, used the concept of equipoise to explore scenarios that the microbicide field might face once trial data become available.[1] Take, for example, questions such as these:

1. *If a microbicide were found to be effective in one trial, would it be ethical to repeat the trial in another population*?

   According to London, the answer depends on how convincing the results of the first trial are and the differences between the two study populations. Some questions that would need to be asked:

   - Are the results of the first trial so robust as to leave no doubt about the effectiveness of the intervention?
   - Might methodological concerns over the first trial leave at least some experts unconvinced as to the findings?
   - Are the differences between the two populations or two trials sufficiently significant so that equipoise may exist for one but not the other? In other words, is there still uncertainty whether the microbicide would be effective in a different population—for example, one with more frequent sex, lower rates of STDs, and so forth?

   The "best" product or intervention for some is not necessarily the best for everyone. What's best for someone will hinge on that person's individual characteristics, environment, problems, and preferences in regard to the existing options—for example, ease of use or sensitivity to side effects. Significant differences in populations may create equipoise in the new trial situation—that is, uncertainty about whether the experimental product shown to be effective in one trial would really be better than the control arm for the new study population. In this situation, it would not be unethical to repeat the trial, with a placebo and standard prevention package in the control arm.

2. *In the case of a microbicide being shown to be effective in one trial, would it be possible to conduct a trial of a second microbicidal product in which the control arm is given condoms and a placebo, not the first microbicide*?

   Equipoise requires that no other method exists that would be a preferable option over any of those in the trial, including the placebo used in the control arm. The key questions would be:

   - After consulting with experts in the field, would a decision-maker have considerable doubt about which package would be better for the control arm—that is, the standard package (condoms and counseling) plus the microbicide that had shown effectiveness in an earlier trial, or the same package with a placebo instead of that microbicide?
   - Would withholding the first microbicide allow some infections that would not have occurred if the product had been given to trial participants?
   - Could providing the first microbicide together with condoms result in less

[1] Johnson, AL. Equipoise and second generation trials. Presented at: The International Consultation on Ethical Issues in the Clinical Testing of Microbicides. October 23–24, 2003; Warrenton, Virginia.

overall protection than if condoms and STD treatment only were provided in the comparison arm (for example, because fewer people try to use condoms)?

Implications for future Phase 3 trials: superiority and equivalence trials

Should it prove to be the case that ethics demands that any future microbicides be tested against existing microbicides (plus condoms), doing trials of second-generation microbicides might become extremely difficult and costly. The requirements for future trials will depend on a number of factors, including the degree of effectiveness of the first microbicide, the incidence rate in the study population, and the question the trial is intended to answer.

Generally, once an effective drug or treatment becomes the standard care for a condition, trials of new products are designed to prove that they are either equivalent to or better than the existing treatment. These trials, known as equivalence or superiority trials, require many more participants than do trials comparing a new treatment to a placebo.

To illustrate, Anne Colletti of Family Health International outlined how superiority and equivalence trials of a next-generation microbicide would work.

Superiority trial. If the researchers sought to show that a new microbicide were better than an earlier product, they would first select the degree of superiority they hoped to be able to measure (that is, the percentage that the second product is expected to be more effective when compared with the first). Assuming that the first microbicide, used as a control, is 33 percent effective and the trial is designed to show that the new product would be 33 percent more effective—or 55 percent effective compared to a true placebo—the trial would have to enroll 7,000 to 10,000 participants to achieve 80 to 90 percent power to detect the effect.[2] If the control were a placebo and condoms, instead of the first microbicide and condoms, the number of participants would be only 1,000 to 2,000.

Equivalence trial. If the goal were to show that the new product is essentially no worse than the first in terms of effectiveness, the researchers would choose a "targeted margin of noninferiority."[3] For example, if the first microbicide offered in the control arm of the study is 33 percent effective and the targeted margin of noninferiority is 10 percent, the number of participants would have to be in the range of 88,000 to 150,000 to achieve 80 to 90 percent power.[4] If there is a question about how effective the first microbicide might be in the population of the new trial, drug regulatory authorities may require both an "active control" (the first microbicide) and an "inactive control" (a placebo arm). Adding a third arm to the trial would increase the number of participants even more.

[2] This estimate makes a number of other assumptions about the trial and the trial site—for example, a 5 percent HIV incidence rate. A trial with 80 to 90 percent power to detect a 33 percent more effective product means that the trial has an 80 to 90 percent chance of detecting the effect, if it is there.

[3] The reasons that it might be worth looking at additional products with roughly the same level of effectiveness are many. A new product might offer advantages, such as being protective against other STDs, contraceptive/noncontraceptive, longerlasting, or lower cost.

[4] This trial would rule out that the new product is less than 26 percent effective.

As is the case with most of the toughest issues regarding the clinical testing of microbicides, answers to questions about future trials are neither straightforward nor obvious.

- Who makes the decisions about the requirements of these later effectiveness trials—for example, the degree of superiority or the margin of noninferiority, the strength of evidence needed, the appropriate control?
- What messages should be given about effectiveness in the informed consent process?
- Who will pay for these subsequent trials, and what are the implications for overall resource allocation?
- How can the concern for safety and the regulatory process best be balanced with the need to expand access to potentially life-saving products?

As the first products enter Phase 3 trials (and many more are in the pipeline), the most daunting question may be how to prioritize which products should move into effectiveness testing. What to do after one or two products show some, even if limited, effectiveness? Meanwhile, the HIV epidemic is a "moving target." It continues to evolve, affected by population movements, vaccines, therapeutics, and other factors. A microbicidal product that is relatively effective, for example in 2010, may not be as effective five years later—for example, if viral resistance develops against an antiretroviral drug used in the microbicide.

10. After the Trial: Continued Access and Post-Approval Studies

Post-trial access

According to international guidelines such as the Declaration of Helsinki and the European Group on Ethics in Science and New Technologies,[1] those who participate in clinical trials should receive continuing access to experimental products that are shown to be effective. This obligation is based on an ethical argument that no one should be withdrawn from a method or medication shown to be beneficial to her or him—all the more in light of the participant's willingness to assume risk as a contribution to the research. Ideally, effective interventions would be provided through the national health system of the country hosting the research. But that seldom happens in practice, especially if the new product is costly.

Obstacles other than cost can impede the research participants' continuing access to experimental products—for example, the time lag between conclusion of the trial and product approval by regulatory authorities. In most cases, additional trials are required before a new drug is approved for licensing. And even where regulatory hurdles are not at issue—for example, products approved for another use that are already available—many questions remain:

- *Who* has the obligation to provide the product or treatment—the study investigators, the sponsor, or the host country?
- Who will pay for it?
- How firm and far reaching does the ethical commitment have to be (for example, cash in the bank to pay for the product)?

As acknowledged by the Nuffield Council on Bioethics, "If researchers or sponsors were categorically required to fund the future provision of interventions, either to participants in the study or to the wider community, many would be likely to cease supporting research. In particular, sponsors from the public sector are unlikely to be able to bear the costs involved without curtailing other research (p. 40)."[2]

This scenario is likely to be especially problematic in the case of HIV treatment trials. The burden imposed by continuing provision of ART is even greater in treatment trials than with prevention trials because trials testing the safety and effectiveness of different treatment regimens in developing countries involve many more HIV-positive individuals than those testing vaccines or

[1] European Group on Ethics in Science and New Technologies. Opinion number 17 on the ethical aspects of clinical research in developing countries, January 2003; Available at: http://europa.eu.int/comm/european_group_ethics/docs/avis17_en.pdf.

[2] Nuffield Council on Bioethics. The ethics of research related to health care in developing countries: A follow-up discussion paper. London: Nuffield Council on Bioethics; 2005.

microbicides. In some prevention trials, fewer than 100 individuals might be expected to become infected during the course of the trial—far fewer than would likely be enrolled in a treatment trial. As a result, the need to sustain long-term ART at former treatment trial sites could easily overwhelm the donors' research budgets.

At the conclusion of trials, investigators should also anticipate the emotional and psychological needs of the participants. In South Africa, staff and participants in the Population Council's Phase 2 microbicide trial reported that some women felt "dumped" or abandoned at the end of the trial. Even among those who had been screened out of the trial, many maintained continuing expectations of trial staff. Consultation participants agreed on the need to not create expectations for continuity that cannot be met. Participants must carefully be "weaned" off the program. In this context, it is particularly important to strengthen local services to which participants can be referred.

Phase 4 studies

Once clinical trials have offered convincing evidence of a product's effectiveness, the licensing process begins. Until a product has been approved and is licensed, it cannot legally be made available, at least according to US regulations. The only way to continue to offer the product to the study participants, or to others, is to initiate a Phase 4 study. At this point, the data collection requirements are reduced and only "adverse events" are reported. Since one of the objectives is to expand access, everyone is given the product and there is no control arm. Phase 4 studies create the opportunity to continue to monitor safety, adherence, and effectiveness; to refine dosing recommendations; and to experiment with different applicators and counseling messages.

Some questions about Phase 4 studies:

- How long should they last? Two years? Five years? Until the product is licensed and available locally?
- What should participants be told about safety and effectiveness in the informed consent process?
- Who will provide the resources, and what are the tradeoffs and opportunity costs for financing of other trials?
- If Phase 3 study populations were rolled over into Phase 4 trials to not interrupt access, those sites would not be available for Phase 3 trials of other products. Would this be acceptable given the limited trial site capacity?

Other options for expanded access while waiting for licensing might include an Investigational New Drug Application[3] in which a new treatment product, which has been shown to be effective but has not yet been approved, is made available to people with life-threatening conditions for which no other alternatives are available. A similar parallel track allows a method under investigation to be provided to people too sick to enter clinical trials. Both of these strategies are justified for extremely ill individuals with no other recourse, so they may not be adaptable for prevention technologies.

After approval, Phase 4 studies may be implemented to consider special safety considerations or to look at effectiveness in

[3] An Investigational New Drug Application is a request to the FDA to allow a drug or product that is still in the research process to be given to humans.

different populations. The International Conference on Harmonization of Technical Requirements[4] recommends that researchers explore how a drug or treatment would act among different ethnic or age groups. This would include, for example, looking at the way a product would be absorbed or metabolized given "intrinsic factors," such as genetic differences, body weight, and organ functions. It also entails consideration of "extrinsic factors" in the environment or culture of the study population, such as climate, exposure to pollution, diet, tobacco use, medical practices, socioeconomic factors, and educational status.

Where is the end of the road?

Approval and licensing is far from the end of the road. As one Consultation speaker remarked, "Once we get to regulatory approval and can sigh with relief, we'll only be halfway there!"

What comes next? The introduction of any new pharmaceutical product poses a challenging new array of problems: manufacture, marketing, distribution, acceptability, and cost to consumers.[5] Guidelines must be developed for using the product, training curricula developed, and informational materials in multiple languages for the most- and least-sophisticated of audiences. Local regulatory requirements must be met. The logistics of procurement, storage, distribution, and service delivery infrastructure must be handled.

For some new products—for example, contraceptives—issues such as these were typically first worked out in pilot districts of a few countries and then scaled up. Yet some questions regarding introduction and access to future microbicides can and should be addressed now. For example, we could conduct research to understand and anticipate the concerns of intermediaries—government functionaries, pharmacists, and health professionals, the key people who will eventually mediate between the product and users. Programmatic and logistical needs can be explored. Studies conducted now can help to identify user attitudes across cultural settings. The wealth of materials that have been developed for informed consent can be adapted and tested for use in counseling situations.

Many questions are simply not answerable, and they will not be until an actual product with known characteristics is in hand. Yet once another microbicide is available, it can and should be more than "just another product." As the development of microbicides has already shown, technology can serve to raise ethical issues ranging from do-no-harm to social justice; and beyond protecting and empowering individual women, they can raise local standard of health care. Whatever else may be uncertain, the need for advocacy around issues of gender power, resource distribution, and access will continue unabated.

[4] Interestingly, although the International Conference on Harmonizaiton developed guidelines for evaluating "ethnic factors," as well as geriatric and pediatric standards, they have not developed any specific guidelines for the inclusion of women in research.

[5] McGrory E, Gupta G. *Preparing for Microbicide Access and Use*. Report of the Access Working Group of the Rockefeller Microbicides Initiative. New York: Rockefeller Foundation; 2002. Available at: http://www.global-campaign.org/clientfiles/rep6_preparing.pdf.

11. Conclusions and New Questions

As anticipated, the Consultation on clinical testing of microbicides raised as many questions as it answered. Yet everyone agreed that a necessary step was taken to better frame the issues and sharpen the terms of an evolving debate. Despite the healthy range of opinion and recognition of the continuing need for reflection and work, the group did arrive at several important points of consensus. Specifically, the following points were endorsed.

1. Researchers have a special, though not exclusive, obligation to the health and well-being of trial participants. In accordance with the principle of reciprocal justice, it is appropriate for research participants to have access to services or benefits that may not be available to others.

2. Nonetheless, investigators and sponsors must avoid undue exacerbation of local inequities in access to care. Since social change is incremental, all progress necessarily introduces temporary inequities. But investigators must remain attentive to this dynamic and seek to minimize negative consequences that could arise from some benefits being selectively available to trial participants.

3. Researchers and sponsors should use microbicide trials as an opportunity to strengthen and improve the local standards of care. Trials can act synergistically to improve local care while simultaneously advancing medical knowledge. The minimum objective should be to ratchet up care in a stepwise fashion to reduce global disparities in access to health care.

4. Trial implementation should seek to build upon and strengthen the capacity of local laboratories, facilities, clinics, and providers. A community should be left better off than before the trial began.

5. Providing access to medical care and services beyond those necessary to conduct the trial should not in themselves be construed as *undue* inducements. Inducements become morally problematic only when they become so appealing as to impair participants' ability to exercise proper judgment or cause them to ignore obvious risks.

6. Microbicide trials should be respectful of existing relationships and networks and attempt to minimize disruptive presence on the community and local services.

7. Microbicide researchers should invest in authentic partnerships with the community, and they should seek community input into decisions around fair benefits for trial participation, ensuring informed consent, reducing stigma, and other trial-related matters.

8. In consultation with the community, researchers and sponsors should develop and disseminate transparent plans on which health care benefits will be provided during and after the trial. Referral arrangements should be concretized through formal Memorandums of Understanding with local facilities.

9. Researchers are not alone in their responsibility to meet the health-related needs of trial participants. The obligation of researchers is to ensure that those enrolled (and screened) in their trials have access to adequate health care, not necessarily to provide it themselves. Nonetheless, researchers should use the resources and power they do command to alleviate suffering whenever and wherever possible.

10. Sponsors and study teams should consider developing formal exit or transition plans to help prepare trial participants and communities for the eventual closure of the trial. Such plans should anticipate the impact of trial completion on local services, arrange for any on-going obligations to participants, and prepare women emotionally for their departure from the study.

11. Moreover, researchers and advocates should leverage resources not related to the research to benefit trial participants and host communities. Research networks, for example, could hire dedicated staff to mobilize non-trial-related resources from private foundations; local government; the Global Fund to fight AIDS, Malaria and Tuberculosis (the Global Fund); or other initiatives to supplement those provided by the trial. A trial advocate could negotiate locally with the national AIDS control board to give the trial community preferential access to ART as the government rolls out its program treatment program.

In addition, the group recommended further in-depth work on several complicated issues discussed during the meeting. These include:

1. Questions related to establishing safety and effectiveness of microbicides in younger adolescents.
2. Issues around men and clinical trials—how to address men's legitimate concerns about safety and cultural expectations of male authority without undermining women's autonomy.
3. Teasing out the ethical and scientific issues posed by the testing of second-generation products.
4. Mechanisms for ensuring access to ART for individuals who seroconvert during trials.

Appendixes

Appendix A: *Participant List*

Appendix B: *Consultation Agenda*

Appendix C: *Selected Readings on Ethical Issues in Microbicide Development*

Appendix A

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International Consultation on Ethical Issues in the Clinical Testing of Microbicides

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October 23–24, 2003

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Appendix B

CONSULTATION AGENDA

Pre-Meeting on Clinical Trials and Ethical Reasoning

***October* 22, 2003**
PATH
1800 K Street, NW, Suite 800
Washington, DC

Prior to the consultation the Global Campaign for Microbicides sponsored a one-day pre-meeting on clinical trials and ethical reasoning. This course, now available upon request, is designed to familiarize participants with the basics of clinical trial design; provide background data on ethical guidance and principles; and provide an opportunity, through case studies, to apply these principles in practice.

1:00 to 1:30 **Welcome and Introductions**

1:30 to 2:15 **Overview of Clinical Trials**

2:15 to 2:50 **Introduction to Ethical Reasoning (Part 1)**

3:00 to 3:30 **Informed Consent Case Study**

3:30 to 3:45 **Ethical Reasoning (Part 2)**

4:00 to 5:00 **Vaccine Trial Case Study**

International Consultation on Ethical Issues in the Clinical Testing of Microbicides

***October* 23, 2003**
Council on Foundations
1828 L Street, NW, Suite 505
Washington, DC

Day One:

8:30 **Welcome and Introductions**
Kim Dickson, Reproductive Health Research Unit, South Africa
Steering Committee, Global Campaign for Microbicides

9:00 **Contextualizing the Field Since the 1997 Ethics Consultation**
Lori Heise, Director, Global Campaign for Microbicides

Meeting goals and agenda; history of the earlier consultation; shifts that emerged in thinking and strategy because of the 1997 *consultation; significant events that have occurred since that time; and the evolution of* HPTN *ethics guidance.*

9:15 **Design Issues in Clinical Trials of Microbicides**
Alan Stone, International Working Group on Microbicides, UK

Basic introduction to the design of microbicide trials; clinical trial pathway for microbicides; and discussion of key challenges: finding a placebo; selection of trial populations. Why are most microbicide trials in the developing world? Measuring effectiveness versus efficacy; and challenges of measuring sexual behavior, gel and condom use. Current controversies: one control arm or two? Length of participant follow-up.

9:45 **International Research Ethics and Debates**
Carel IJsselmuiden, University of Pretoria, South Africa

Historical origins of modern bioethics. Introduction to ethical reasoning and key principles. What makes research ethical? Basic concepts and principles; debates over universal versus pluralistic standards of care; and recent controversy around placebo-controlled trials. Dealing with culture and community. What makes HIV *prevention trials different–stigma, healthy individuals, etc.?*

10:30 **Session 1: Informed Consent: From Theory to Practice**
Marge Chigwanda, UZ-UCSF Collaborative Research Program, Zimbabwe
Cynthia Woodsong, Family Health International, USA

Discussion of the microbicide field's efforts to address informed consent. Issues that remain; examples of creative approaches to achieving and sustaining informed consent, including videos, assessment of comprehension, etc.

11:30 **Session 2: Benefits and Burdens to Participants and Communities—Conceptualizing Fair Benefits**
Reidar Lie, National Institutes of Health, USA/Norway

Evolution of ethical thinking on this issue; insights from guidance; balancing risks and benefits; NIH *consultation on fair benefits; balancing benefits and "undue inducement;" What is the difference between inducement and "undue" inducement? Ensuring reasonable availability of interventions post trial.*

1:15 **Session 2: (Continued): Benefits and Burdens**
Evaluating Carraguard–A look at burdens and benefits from multiple vantage points
Heidi Jones, Population Council–General reflections
Barbara Friedland–Population Council–Phase II coordinator
Mabitso Marumo–counseling coordinator, MEDUNSA
Esther Maleka, Former Phase II trial participant, South Africa
Discussant: Alex London, Carnegie Mellon University

3:00 **Session 3: Defining the Standard of Care**
Considering Standard of Care from a Research Ethics Perspective
Liza Dawson, Fogarty International Center

Multiple uses of this concept; insights from Guidance; context of global health inequities; moral basis of standard of care debates; health care versus research ethics; international debates and tensions (local standard; best proven; highest attainable and sustainable; ratcheting up).

Ethics Meets the Rough Grounds
Kathleen MacQueen, HPTN Ethics Working Group

Defining the range of care issues at stake (beyond ARVs*). Insights from* FHI's SOC *survey at* HPTN *sites—variations between care available in different settings. Findings of how* HPTN 035 *participants conceptualize "fair."*
Discussants: Anatoli Kamali (MRC-Uganda), Miriam Katende (TASO), Promise Mthembu, ICW.

Day Two:

8:30 **Session 4: Men, Ethics and Microbicide Trials**
What are the issues? How is the field responding?

Panel discussion:
Busisiwe Nkala, Soweto, South Africa
Neelam Joglekar, Pune, India
Michael Gross, consultant, USA
Experience from audience members

Concerns about penile safety; expectations around men's right to control female behavior; issues around trials "excluding" men, partner consent, etc.
Discussants: Ethical- and rights-based reflections on men, culture, and trials
Carel IJsselmuiden–University of Pretoria
Brendon Christian–Gender AIDS Forum, South Africa

10:15 **Session 5: HIV Treatment in the Context of Prevention Trials**
Introduction to On-Going Deliberations and Debates
Lori Heise, Global Campaign for Microbicides

Providing ART: Examining the ethical arguments
Catherine Slack, University of Natal, South Africa

Scientific and Practical Challenges of Treating HIV Infections
Paula Munderi, MRC Uganda

WHO/UNAIDS Consultation on ART in Prevention Trials
Eduard Beck, McGill University, Canada

Opportunities to Partner and Leverage Outside Resources
Camille Massey, International AIDS Vaccine Initiative
Discussion

1:30 **Session 6: Establishing Safety and Effectiveness in Younger Adolescents**

Younger Adolescents: Do We Need Separate Data?
Barbara Moscicki, Division of Adolescent Medicine, UCSF

Ethical Reflections on Enrolling Adolescents in Trials
Audrey Rogers, NICHD Adolescent Clinical Trial Unit

A View from Botswana
Dawn Smith, BOTUSA Project, Gaborone, Botswana
Discussion

3:00 **Session 7: Ethics of Second-Generation Microbicide Trials**
If a RCT demonstrates some effectiveness for a first-generation product what implications would this have on the design of future trials. What role can post-approval trials play? Under what circumstances could we ethically do a confirmatory trial in a different setting?

Equipoise and the Issue of Second-Generation Trials
Alex London, Carnegie Mellon University

Scientific Challenges in Testing Next-Generation Products
Anne Coletti, Family Health International

The Potential Role for Post-Approval Studies
Forrest Greenslade, Consultant
Discussant: Tim Farley, World Health Organization

5:00 **Summary Reflections and Rapporteur Report**
Kim Dickson, South Africa

Appendix C

SELECTED READINGS ON ETHICAL ISSUES IN MICROBICIDE DEVELOPMENT

Contextualizing the Field Since 1997

Heise L, McGrory E, Wood S. *Practical and Ethical Dilemmas in the Clinical Testing of Microbicides: A Report on a Symposium*. New York: International Women's Health Coalition; 1998.

MacQueen K, Sugarman J. Back to the rough ground: working in international HIV prevention as ethical debates continue. IRB: *Ethics and Human Research*. 2003;25(2): 11–13.

MacQueen K, Sugarman J. HIV *Prevention Trials Network: Ethics Guidance for Research*. Arlington Virginia: HPTN Ethics Working Group; 2003.

Lo B, Bayer R. Establishing ethical trials for treatment and prevention of AIDS in developing countries. *British Medical Journal*. 2003;327:337-339.

Background Materials on Microbicides and Clinical Trials

Harrison P, Rosenberg Z, and Bowcut, J. Topical microbicides for disease prevention: status and challenges. *Clinical Infectious Disease*. 2003;36:1290–1294.

Stone A. Clinical trials of microbicides. *The Microbicide Quarterly*. 2003;1(2):13–18. Available at: http://www.microbicide.org/microbicideinfo/reference/final.TMQ.jul.aug.sep.2003.pdf

Background Materials on Biomedical Ethics

Emanuel E, Wendler D, Killen J, Grady C. What makes clinical research in developing countries ethical? The benchmarks of ethical research. *Journal of Infectious Diseases*. 2004;189:930–937.

Nuffield Council on Bioethics. The ethics of research related to health care in developing countries: Follow up discussion paper. London: Nuffield Council; 2005. Available at: http://www.nuffieldbioethics.org/fileLibrary/pdf/HRRDC_Follow-up_Discussion_Paper001.pdf

Informed Consent

Lindeggar G, Richter LM. HIV vaccines trials: critical issues in informed consent. *South African Journal of Science*. 2000;96:313–318.

Molyneux CS, Wassenaar DR, Peshu N, Marsh K. Even if they ask you to stand by a tree all day, you will have to do it (laughter)…!: Community voices on the notion and practice of informed consent for biomedical research in developing countries. *Social Science and Medicine*. 2005, 61: 443-454.

Standard of Care

Benetar SR, Singer PA. A new look at international research ethics. *British Medical Journal*. 2000;321:824–826.

Lie RK, Emanuel E, Grady C, Wendler, D. The standard of care debate: the Declaration of Helsinki versus the international consensus opinion. *Journal of Medical Ethics*. 2004; 30:190–193.

Shapiro K, Benetar SR. HIV prevention research and global inequality: steps towards improved standards of care. *Journal of Medical Ethics*. 2005;31:39–47.

HIV Treatment in the Context of Prevention Trials

Berkley S. Thorny issues in the ethics of AIDS vaccine trials. *The Lancet*. 2003;362.

Bass E. HIV *Treatment in the Context of* HIV *Prevention Trial*. Proceedings of a meeting cosponsored by the Global Campaign for Microbicides and the International AIDS Vaccine Initiative, Washington DC, February 28, 2003. Available at: http://www.global-campaign.org/clientfiles/ethicsreport.pdf

Slack C, Stobie M, Milford C, Lindegger G, Wassenaar D, Strode A, IJsselmuiden C. Provision of HIV treatment in HIV preventive vaccine trials: A developing country perspective. *Social Science and Medicine*. 2005;60:1197–1208.

WHO/UNAIDS. Treating people with intercurrent infection in HIV prevention trials: report of a WHO/UNAIDS consultation. ***AIDS.*** 2004;18(15):W1-W12.