

Intertwining Biomedical Research and Public Health in HIV Microbicide Research

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Finding an effective microbicide that could substantially lower women's risk of acquiring HIV infection is an ethical imperative. Women and girls continue to be disproportionately affected by HIV in sub-Saharan Africa. Ethics guidelines for conducting preventive HIV microbicide trials call for steps that intertwine biomedical research and public health. Ethical considerations include adequate studies of the safety of microbicides, the use of placebo controls in future trials once a microbicide is shown to be effective, whether leftover microbicide from a trial that demonstrated efficacy should be made available to the public or used in the control group of a future trial, what preventive measures and treatment should be provided for trial participants during and after the research, and what constitute 'fair benefits' to the community or country when a trial is completed. The Global Campaign for Microbicides conducted a study of the benefits being provided to participants in microbicide trials and others, and found substantial evidence that researchers and sponsors are meeting the obligations stated in ethical guidelines. A cautionary tale of an HIV prevention trial that was prematurely halted demonstrates the need for engagement with the community where trials are carried out.

One of the greatest public health challenges of our time is reducing the incidence of HIV disease, along with the related suffering and stigma. Since behavioral interventions have been unsuccessful in stemming the tide of the epidemic, biomedical prevention remains the best single hope. An effective method to prevent HIV infection is needed for all people at high or moderate risk, wherever they may live. Since biomedical prevention trials must involve large numbers of people in order to attain valid results, they must be conducted in developing countries as they have the highest burden of disease. Yet it is in these resource-poor settings that strict adherence to key ethical guidelines may be hardest to achieve. This is because state-of-the-art prevention packages and ancillary medical care are often not readily available in those settings.

To date, research on HIV vaccines, microbicides and drugs that have demonstrated efficacy in treating HIV infection have not yielded a product for prevention approved by a regulatory authority. Nevertheless, advance preparation is ethically required even if future research results in an only moderately effective preventive method. Ethical guidance is needed to determine whether the design of subsequent trials may involve a placebo control, whether an effective preventive method should be provided for all participants in future trials

and whether a public health obligation requires that an effective biomedical prevention resulting from a clinical trial be provided to the community where the trial takes place. This article addresses these questions for microbicide trials in which women are the participants. The main thesis is that the goals of public health and clinical research should be considered compatible and therefore, should be mutually reinforcing. Public health practice aims at protecting and promoting population health, whereas clinical research is designed to produce generalizable knowledge that can contribute to the health of the population. Existing ethical guidance for HIV biomedical prevention research points in the right direction, and researchers and sponsors should follow its provisions. However, some questions can be answered only in the specific context in which they arise.

Public Health Needs and Safety in Microbicide Trials

According to UNAIDS, women, and especially younger women, are increasingly at risk for acquiring HIV. 'Women and girls continue to be disproportionately affected by HIV in sub-Saharan Africa. Throughout the region, women account for 60 per cent of all HIV

infections. Young women between the ages of 15 and 19 are particularly vulnerable to HIV. In Kenya, young women are three times more likely to become infected than their male counterparts' (UNAIDS Fact Sheet, 2009). It is evident from these brief statistics that a growing injustice exists in the proportion of women who become newly infected compared with men in sub-Saharan Africa. In addition to the disproportionate number of African women now infected or at risk, younger women are typically disempowered, unable to negotiate safe sex with regular partners or occasional ones, and may be engaged in transactional sex to support themselves or their children. It is clear that a great need exists for a safe and effective method for preventing HIV infection.

Since the participants in HIV prevention trials are healthy individuals, safety concerns are of paramount importance. There is always a risk that an experimental product will cause unanticipated harm to research subjects.

To the surprise and dismay of researchers, in early 2007 two microbicide trials using a cellulose sulfate compound were halted prematurely when data in one of the studies showed a higher rate of HIV infection in women in the experimental arm than in women in the control group. The study was a randomized, controlled trial testing the experimental product against a placebo gel for effectiveness against vaginal transmission. This trial was stopped following the recommendation of the Data and Safety Monitoring Committee when the committee reviewed preliminary data, which indicated that more women in the experimental arm had HIV seroconversions compared with the placebo arm of the trial (Ramjee *et al.*, 2007). A similar episode had occurred several years earlier in a study using another product (nonoxynol-9) in general use as an effective spermicide to see whether it would protect against HIV infection. In that study, conducted in several African countries, there was also an increase in HIV infection among women who used the product more than three times a day (Horwood, 2007).

In those two episodes the harm caused by the experimental product made the subjects *more* susceptible to the very disease the intervention was designed to prevent. So even when animal studies have indicated that the product is safe, there are still safety concerns for women enrolled in early phases of microbicide research. Once studies in the early phases of clinical research suggest that a product is safe, the purpose then becomes to test its efficacy. For prevention trials, this typically requires very large numbers of participants, usually healthy individuals at high risk of HIV infection. One

group that regularly engages in high-risk behavior is sex workers, whose rates of HIV infection remain high all over the world. But as this is a marginalized group, engaged in most places in an activity that is illegal as well as socially ostracized, the ethical, social and legal concerns of recruitment and involvement in research are magnified.

Every new microbicide must be tested first for safety in a small number of volunteers. But even products demonstrated to be safe in one population or circumstance still have to be tested for safety in others. Additional research that may have to be done after the first trial in which a microbicide is shown to be safe are tests of safety in high frequency use, which is the case for sex workers; safety for rectal use (especially for men who have sex with men, but also for heterosexual couples who practice anal sex); safety in pregnancy in women; and safety in adolescents. The same repetition would normally be required for efficacy studies, but that poses a familiar ethical problem. Once a microbicide is found to be efficacious in one population or situation, the perennial debate about the ethics of a placebo control is sure to arise when trials are proposed for different populations or different circumstances.

Control Groups once a Microbicide Is Shown to be Efficacious

The first dilemma researchers will face when efficacy is demonstrated for a microbicide is whether it is ethically acceptable to use a placebo control in a subsequent trial. This revisits a controversy in research ethics that has raged for many years. The *Declaration of Helsinki* (World Medical Association, 2008) and the *CIOMS International Ethical Guidelines* (Council for Organizations of Medical Sciences, CIOMS, 2002) address this question for all preventive, diagnostic and therapeutic methods. A UNAIDS/WHO publication is devoted specifically to ethics in HIV biomedical prevention trials (the document covers vaccines and preventive medications as well as microbicides). Guidance Point 15 says: 'The use of a placebo control arm is ethically acceptable in a biomedical HIV prevention trial only when there is no HIV prevention modality of the type being studied that has been shown to be effective in comparable populations' (UNAIDS/WHO, 2007: 51).

This guidance point is controversial from a methodological perspective. A clinical trial comparing an experimental preventive method with a proven method takes longer to complete and is more costly, and the results may be much more difficult to interpret than a placebo-controlled trial. As a report from a meeting

organized by WHO and UNAIDS in 2009 observes: ‘Depending on the product’s particular mechanism of action it may not be possible to separate out the effect of the test product (for example, providing a vaginal product in a trial of another vaginal product, or an ARV-based prevention method in a trial of another ARV-based method)’ (McGrory and Farley, 2009).

Yet from both a public health perspective and the ethical imperative to minimize risks to research subjects, it would be wrong to fail to provide an effective microbicide to the control group. The UNAIDS/WHO guidance point has an apparent loophole in the exceptions included in the rule. This is one of the questions that can be answered only in the specific context of a proposed future trial: how to interpret the phrase ‘of the type being studied that has been shown to be effective in comparable populations’. What ‘types’ of microbicide would count as eligible or ineligible? And what is the criterion for comparability among populations?

This latter question is especially important because of the different ways in which populations may be considered to be non-comparable. Are African American women in major urban centers in industrialized countries comparable with women in sub-Saharan Africa or to Jamaican women? Are women who have multiple partners (such as sex workers) comparable with women who have one or a small number of partners who may be HIV-infected? And are women who engage in harmful traditional practices common in parts of Africa comparable with women who do not? An example of the latter exists in a number of sub-Saharan African cultures in which men have a strong preference for ‘dry sex’ and women comply with this desire by engaging in a variety of practices designed to tighten or dry out the vagina. Such practices are believed to make women more susceptible to HIV infection (HIV This Week, 2009).

The idea that future clinical trials of a microbicide would require a placebo group when an effective microbicide exists outside the trial is unthinkable to many people. Controversy has continued to rage since 1997 when preventive maternal-to-child HIV transmission (PMTCT) studies conducted in developing countries included a placebo control. As has been widely discussed, a successful preventive regimen existed and was available in the USA and Western Europe, and it would have been ethically unacceptable to have a placebo group in any trials in the industrialized countries. A future debate is almost certain to occur when the first microbicide (or HIV-preventive vaccine) is demonstrated to be efficacious and licensed for use.

Access will vary depending on where women live. One difference will be between trial participants in the

countries that participated in the first successful microbicide trials, and those in the control group in trials of the next candidate microbicide that take place in a different country. Guidance Point 19 of the UNAIDS/WHO document calls for making ‘available as soon as possible any biomedical HIV-preventive intervention demonstrated to be safe and effective... to all participants in the trials in which it was tested...’ (p. 60), so this would include the subjects in the placebo group in the first trial, as well as those in the experimental arm who received the microbicide shown to be effective.

The impossibility of arriving at a scientifically valid conclusion is a good reason why a placebo group might be necessary in future microbicide trials. But if this methodological constraint does not exist, a debate is bound to arise that pits the concerns of research ethics against those of public health. Defenders of a placebo-controlled trial argue that the shorter time it takes will enable a successful product of the research to be available more quickly than a trial with an active comparator. Therefore, many more people in the community will have access much sooner to a successful preventive HIV microbicide. Defenders of using a proven, effective microbicide in the control group argue that one of the ethical requirements in research is to minimize risks to subjects. Clearly, providing a proven HIV prevention to the control group adheres to this requirement, whereas providing placebos does not. Placebo defenders are likely to reply that if one compares the number of people in a placebo group who do not get the proven effective microbicide with the number of people in the community who would be denied access to an effective microbicide if the longer trial is conducted, the latter number would be much larger. Therefore, a straightforward utilitarian calculation appears to favor a shorter trial that can yield public health benefits to more people. A potential flaw in this argument is that the trial might not result in a successful product, so the placebo group, the experimental group and the community would all lack access to an effective preventive HIV microbicide. Only hindsight can determine whether the placebo arm is worse than, equal to or safer than the experimental arm. This is true of all clinical trials that meet the requirement of clinical equipoise at the time the study is initiated.

A different ethical challenge is bound to arise when a clinical trial has demonstrated the efficacy of a new microbicide. It is likely that only a small amount of the experimental product will be left over following a trial since the manufacturer would not have scaled up production beyond what would be needed for the trial itself. But whatever is left over could be used in one of

two ways. It could be used as a comparator, instead of or in addition to a placebo in a subsequent trial; or leftover microbicide could be used for prevention among women at high risk of infection in the community where the trial was conducted. This choice requires setting priorities when there is only a small amount of a safe and effective product for which there is urgent need. A pressing question is who should set these priorities and whether some sort of community engagement should be an integral part of the process. Should the public health benefit, although limited, outweigh the scientific need to use the leftover microbicide in the next clinical trial, and who should decide?

All the unanswered questions about the ethics of placebo controls and use of leftover product from biomedical prevention trials call for an acceptable approach to the procedural, 'who should decide' question. The UNAIDS/WHO Guidance Point 15 provides a sound ethical and public health presumption in favor of providing an effective microbicide to the control group in future trials. Both organizations (UNAIDS and WHO) frequently collaborate in a procedural approach to ethical, legal and regulatory issues that arise in connection with HIV prevention research. Together they organize and conduct regional consultations involving participants from the scientific, bioethics and public health communities, as well as members of advocacy groups and non-governmental organizations (NGOs). The outcomes of these consultations are meeting reports and recommendations, which are then published on the UNAIDS and WHO websites. This method of involving an array of stakeholders is a better procedure than leaving ethical judgments entirely in the hands of the sponsors of research or experts in clinical trial methodology. At best, however, these consultations provide general presumptions and do not have binding force for taking decisions in any specific biomedical prevention trial.

Standard of Prevention, Standard of Care

A second ethical question for future microbicide trials is what should be provided to all participants in a biomedical prevention trial to reduce the risk of their becoming HIV-infected as a result of their behavior, not the experimental product itself. Forward-looking ethical guidance goes beyond traditional harm reduction interventions in public health without abandoning those methods. The ethical concerns in this case are similar to those of placebo controls and are equally if not more worrisome to researchers. The UNAIDS/WHO

document has guidance on this issue using the new term, 'standard of prevention', in place of 'risk reduction'. Guidance Point 13 says: 'Researchers, research staff, and trial sponsors should ensure, as an integral component of the research protocol, that appropriate counseling and access to all state of the art HIV risk reduction methods are provided to participants throughout the duration of the biomedical HIV prevention trial' (p. 45). When this point was introduced at several conferences, researchers were astounded, and objected that following the guidance would make it virtually impossible to study whether the experimental product is effective. 'Do you really mean *all* state of the art preventive methods?', one participant asked. If an effective preventive vaccine is licensed when microbicide trials are still ongoing, does it mean that participants in both the experimental and control groups of a microbicide trial should be offered the vaccine? Both this guidance point and the one regarding placebos create a tension between maintaining the highest ethical standards and ensuring that the design of clinical trials is methodologically capable of reaching valid and accurate results. How to escape between the horns of that dilemma is likely to pit biomedical researchers and trial methodologists against ethicists and, in the case of microbicide research, feminists and advocacy groups. However, an ethical principle in research ethics provides an unequivocal answer: in research involving human beings, risks to subjects must be minimized.

Although the actual determination of what prevention package will be provided to trial participants awaits a demonstration of efficacy of a candidate microbicide (or vaccine), it is useful to see what preventive methods are currently being provided at microbicide trial sites in large HIV prevention trials. This is one way of ascertaining how close actual practice is to the ethical guidance provided in documents like the UNAIDS/WHO publication. It is especially important to be able to respond to critics who have contended that the guidance points in the UNAIDS/WHO document and other ethical guidelines are purely 'aspirational', by which they mean an ideal that is far from what can realistically be achieved. That objection misses the point that there always must be an aspirational aspect to ethics guidance; otherwise, everything would be permanently stalled at whatever is the status quo.

The GCM Study

The Global Campaign for Microbicides (GCM) undertook a broad and detailed study, one of whose goals was 'To explore the microbicide field's progress toward

achieving the ethical aspirations laid out in key ethics guidance documents' (Global Campaign for Microbicides, 2009a). The major finding from the study was that overall, microbicide trials are meeting or exceeding the ethical obligation to provide access to proven HIV-preventive methods, including risk-reduction counseling, provision of male condoms and access to female condoms (when requested). This ethical obligation is precisely what is required by Guidance Point 13 in the UNAIDS/WHO document. By this means, current microbicide trials are intertwining biomedical research with public health practice. The GCM report contains two sets of recommendations: consensus recommendations from the consultation held at the end of the study, and recommendations by GCM staff following the consultations and after their deliberations on the findings and consensus recommendations.

Somewhat confusingly, this report includes several different items under the heading, Standards of Care. The phrase has several meanings in the literature on research ethics. Sometimes it refers to what the control group should receive when an effective product exists outside a clinical trial, as discussed above. (This meaning was adopted following the controversy over the placebo-controlled PMTCT trials in developing countries.) The phrase often also refers to ancillary care and medical treatment of participants in a prevention trial who acquire the target disease while the trial is ongoing (Tarantola *et al.*, 2007). The GCM report does not distinguish between these latter meanings of 'standard of care' and the more specific 'standard of prevention' discussed in the UNAIDS/WHO guidance.

At most of the trial sites the GCM project visited, female condoms were available to participants on request, but unlike male condoms, supplies were not automatically provided to the women. The report acknowledged that more is needed and could be done to incorporate the female condom into the standard prevention package at microbicide trial sites. The consensus recommendation on this point says: 'The female condom should be integrated into the standard prevention package in future and ongoing trials, and provided by sponsors at sites even where they are not available in the public sector' (p. 34). This could have a positive effect on more widespread use of the female condom for prevention, not only among women who have been enrolled in microbicide trials but other women in the community, as well.

The consensus recommendation regarding women who become pregnant during the study is that those women should remain in the study, but presumably no longer use the experimental product. The study

design for all of the microbicide trials examined required that the microbicide gel be discontinued in pregnant women. The GCM recommendation adds a more controversial feature: 'Where abortion is legal, site staff should be trained to counsel women on all options, including termination. Even where abortion is illegal, staff should additionally be trained to counsel on the dangers of unsafe abortion, as well as when and where to seek care in the event of post-abortion complications' (p. 50).

The GCM study found that most trial sites did not initially provide contraception for women for prevention of pregnancy (other than the condoms that were universally distributed). However, there were such high pregnancy rates in these microbicide trials that the study protocol was later amended to include provision of contraception. Acceptance of contraception was voluntary and depended on the women's own values regarding the use of contraception and the chance of pregnancy. The report contains three strong consensus recommendations regarding sexual and reproductive health: the need for counseling and provision of safe, appropriate contraception; site-specific options to terminate pregnancy; and counseling and provision of emergency contraception.

These GCM recommendations on standards of care come very close to what the UNAIDS/WHO ethical guidance document says in its commentary on Standard of Prevention: 'Risk-reduction packages should include provision for family planning, pregnancy and childbirth services. ... Researchers should guarantee that all communities engaged in biomedical HIV prevention trials have state of the art reproductive health care services.' (UNAIDS/WHO, 2007: 45). Critics have complained that it is too high a standard for most clinical trial sites to meet, yet the GCM consultation reached much the same consensus recommendation. Clearly, a recommendation that locations in which these trials occur should have well-developed reproductive health care services benefits the much wider community, as well as the research participants themselves. This is yet another instance of intertwining public health benefits with biomedical prevention research, showing that research ethics and public health should not only be considered compatible but should also be mutually reinforcing. Results such as this have implication for the selection of sites for future microbicide and other prevention trials. If researchers or sponsors are unwilling or unable to provide reproductive health care or other ancillary care services in resource-poor settings, they should choose sites for prevention research in developing countries where such services are already available.

The consensus recommendation on ‘standard of care’ and others in the GCM report indicate that the prevailing view regarding what is owed to participants in clinical trials is beginning to splinter. That view has long maintained that the ethical obligations of researchers and sponsors are to do only what is necessary to conduct the trial safely by minimizing risks and providing safeguards, and to attend to the requirements of voluntary, informed consent and protecting the confidentiality of subjects. This is a minimalist view of research ethics, which has some strong proponents. The position is sometimes cast in terms of the distinction between the obligations of researchers and the obligations of physicians practicing clinical medicine (Miller and Rosenstein, 2003). While it is true that research is not therapy and it is important to avoid the therapeutic misconception (Brody and Miller, 2003), maintaining that distinction does not preclude researchers from providing ancillary preventive or therapeutic methods to trial participants. Since the purpose of conducting prevention research is to produce public health benefits for the population, it is ethically desirable to include these ancillary benefits during the conduct of clinical trials when they are reasonably available.

The GCM report covers two other topics that have been extensively debated. One is providing antiretroviral treatment to women who become HIV positive during a microbicide trial and those found to be positive at the initial screening; the other is continuity of care for women who need care and treatment after a trial ends. Such care and treatment is not limited to antiretroviral medications for women who seroconverted during the trial, but could include treatments for sexually transmitted infections and other conditions that were made available to them while the trial was ongoing. What began as a perceived obligation to research subjects within a clinical trial became transformed into a public health benefit after their participation ended. The findings for access to HIV treatment for women who became medically eligible during the trial showed that unlike ten years earlier, every trial site visited had free antiretroviral treatment services available in the community. Some treatment centers were new, others were overburdened, and still others charged fees for baseline tests required to enter the programs. The GCM report’s consensus statement on this topic calls for future microbicide trials to take concrete steps to improve referral systems and access to treatment for women who are screened out initially because they are HIV positive.

While still a long way from universal access that remains the longer-term public health goal for HIV

treatment (UNAIDS, 2010), progress in making state-of-the-art treatment widely available in resource-poor communities has been impressive. This progress belies the cynical views expressed by commentators less than a decade ago, who sharply criticized as unrealistic ethical guidance that called for the steps now being implemented (Specter, 2003). Better coordination in linking prevention trials with places where HIV/AIDS therapy is already scaled up is one step that can ease the burden of researchers themselves having to struggle in what they increasingly accept as an obligation to participants in HIV-preventive microbicide and vaccine trials.

Post-trial Benefits: from Research to Public Health

The third ethical question in these prevention trials is what obligations exist to provide benefits to the communities where the research is conducted. Three international ethical guidelines for research have roughly similar guidance points regarding post-trial benefits. The relevant portions are the following.

The Council for Organizations of Medical Sciences (CIOMS) (2002: 51) calls for making the successful products of biomedical research available to the population where the research is carried out. Guideline 10 states:

Before undertaking research in a population or community with limited resources, the sponsor and the researcher must make every effort to ensure that:

- the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and
- any product developed will be made reasonably available to that population or community.

The sweeping revision of the *Declaration of Helsinki* in 2000 included this idea for the first time since the Declaration appeared in 1964: ‘Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research’ (Paragraph 19). That left wide open several key questions: What are the criteria for determining likelihood? What degree of likelihood is necessary? What types of results count as benefit? The 2008 revision of the Declaration altered the wording to resemble the CIOMS guideline, but limited the scope of the requirement. Paragraph 17 limits the benefit to disadvantaged or vulnerable communities: ‘Medical research involving a disadvantaged or vulnerable population or

community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.’

The strongest statement in any of the leading guidelines is one that pertains specifically to microbicides and other biomedical HIV-preventive methods: ‘[T]rial sponsors and countries should agree on responsibilities and plans to make available as soon as possible any biomedical HIV-preventive intervention demonstrated to be safe and effective. . . to all participants in the trials in which it was tested, as well as to other populations at higher risk of HIV exposure in the country’ (UNAIDS/WHO, 2007: 60).

Some critics of the 2000 version of the *Declaration of Helsinki* and the 2002 CIOMS Guidelines argued that their requirement for making the benefits of research ‘reasonably available’ was aspirational, aiming at an ideal impossible to achieve in practice. As treatment for HIV/AIDS has scaled up remarkably in the last decade, and other treatments, such as those for malaria and tuberculosis in developing countries have also expanded, that criticism has begun to abate. Instead, another criticism has taken its place. That is the critique mounted by proponents of the ‘fair benefits’ framework.

Fair Benefits Framework

The ‘fair benefits’ framework was developed by participants in a conference held in 2001 (Participants, 2002, 2004). Their target was Guideline 10 of the CIOMS international guidelines. The critique begins with the claim that successful products of research are not necessary for benefits to be equitable. This is chiefly because benefits other than the successful products of research may be valued equally, if not more, by the community where research is conducted. The critique contains a series of separate points leading to the conclusion that benefits other than that of the successful products of research are fair and may be ethically superior to provision of the product itself. The main points in the critique are as follows.

- The requirement does not guarantee that a benefit will be *fair*. For example, there can be research in which the subjects are exposed to great risks, or the sponsors receive enormous benefits.
- In cases in which the risks to subjects are minimal and the benefits to sponsors are also minimal, it could be unjust to require the sponsors to make a successful product available to the population.

- A prior agreement to provide a specific product can constrain the population instead of benefiting it. This is because the population would have to use this specific product even though a better product may come along later.
- By specifying what is to count as a benefit, the requirement to make the successful products of research a fair benefit involves a conception of benefits that is too narrow. Other potential benefits could include training persons who provide health services or construction of clinics, hospitals or other physical infrastructure.
- It is paternalistic for the sponsor or ethical guidelines to specify what ought to be the benefits of research. It implies that officials or the population in the country cannot make their own autonomous decisions.

Although some features of this critique are well taken, several points are seriously flawed. Regarding the first critical objection, it is very rare that a study poses ‘great risks’ to subjects. If such research does exist, it is more than likely to be in the very early stages of a study in which the safety of a biomedical product is being tested. However, the requirement for making the successful products of research available does not apply to phase I research because at that stage, the efficacy of a product cannot be determined and the product may not turn out to be successful after subsequent phases of the research are completed. Moreover, all research regulations and guidelines require the risks to be ‘reasonable’ in light of the anticipated benefits. It isn’t likely that a research ethics committee would approve a study that poses ‘great risks’. On the issue of ‘enormous benefits’ to the sponsors, this already occurs in the case of much research in which the pharmaceutical industry obtains huge profits from its blockbuster drugs.

The critique regarding minimal risks to subjects and minimal benefits to sponsors mistakes the purpose of the ethical requirement. The amount of benefit that a sponsor receives is not relevant to the requirement that the community should receive fair benefits. Commercial sponsors arrange their research portfolios in a way that enables them to offset low profits from some products with the very high profits they obtain from costly products with a huge market. In addition, the level of risks that the subjects undergo is totally irrelevant to the requirement that the community should receive fair benefits. For example, the majority of vaccine trials pose low risks to subjects, especially in phase III (when efficacy is being tested), because earlier phases have normally provided sufficient evidence of safety. Vaccines traditionally have not provided great profits to the sponsors. But

there is wide agreement that vaccines are a product having great public health benefit and should be made available as widely as possible even in low-income countries. Microbicides for HIV prevention may have somewhat higher risks to users than vaccines traditionally have had, but the public health benefits of microbicides are likely to be significant.

The critical objection that a population would be constrained to use a superior product is an example of flawed logic. No one would insist that women use an inferior microbicide when a newer, more effective one becomes available. The solution to this non-problem is to establish appropriate conditions in the prior agreement. The several parties can negotiate their agreement or contract to say what ought to happen in cases where a superior product becomes available later on. In any case, a similar agreement should be made in subsequent research, and the population can then receive the product that is demonstrated to be superior.

The only persuasive objection in the 'fair benefits' critique is that it would be a narrow benefit if successful products were the only possible or allowable benefit. However, a requirement to make the products of research available does not preclude the possibility of also providing other benefits to the community. Women at risk for HIV infection may be perfectly happy for the community as a whole to receive the other types of benefits noted in the critique. But what the women themselves need is an effective microbicide.

Finally, it is true that ethical guidelines have an element of paternalism. Many requirements in ethical guidelines dictate what ought to be done. If the fair benefits approach were adopted, it would be necessary to establish a mechanism by which the population could choose the benefits of research—not an easy task, by any means. If it were left to governmental officials alone to decide what ought to be the benefits of research they allow to be carried out in their country, they could demand money, which they could then use to buy weapons to fight their neighbors. Even a more benign choice could ignore women's needs. It is not likely that women will have sufficient power and authority to argue successfully for their priorities in the face of competing interests in the community.

The fair benefits critique ignores the public health purpose of conducting biomedical research: to prevent, cure or ameliorate diseases in human beings. If research does, in fact, yield successful products, and these are not made available to the population in a resource-poor country but are accessible to people in wealthier countries, there is no ethical justification for conducting the research in the developing country. As one article

notes: '...if the results of a clinical trial are not made reasonably available in a timely manner to study participants and other inhabitants of a host country, the researchers might be justly accused of exploiting poor, undereducated subjects for the benefit of more affluent populations of the sponsoring countries' (Crouch and Arras, 1998: 29).

Community Engagement

A social factor that has implications for the ethical conduct of microbicide trials is the need to engage the community in plans for recruitment of participants, the actual conduct of the trial and follow-up when the subjects' participation has ended. The UNAIDS/WHO ethical guidance document includes a strong recommendation regarding community involvement: 'To ensure the ethical and scientific quality and outcome of proposed research, its relevance to the affected community, and its acceptance by the affected community, researchers and trial sponsors should consult communities through a transparent and meaningful participatory process which involves them in an early and sustained manner in the design, development, implementation and distribution of results of biomedical HIV prevention trials' (UNAIDS/WHO, 2007: Guidance Point 2). UNAIDS also co-authored a companion document that focuses exclusively on community participation and includes detailed practical guidance (UNAIDS/AVAC, 2007).

The aspects of the UNAIDS/WHO recommendation on community involvement that are likely to be problematic are immediately apparent. The guidance calls for consulting communities in the design of a microbicide trial. What should happen if community members object to a placebo arm of a proposed trial when an effective microbicide has been tested and made available in another country? The scientists involved in trial design choose to adopt the 'escape clause' in Guidance Point 15 in this same document, that is, the exception to the placebo rule when an experimental microbicide is being tested in a population different from the one in which an existing microbicide was tested. The scientists will almost certainly win this dispute. Although the guidance point calls for a 'transparent and meaningful process', it is clear that it is a process of consultation, not that of joint decision making about scientific or methodological aspects of a clinical trial.

Guidance Point 2 also calls for consulting with the community on the implementation of an HIV-preventive microbicide trial. A substantial commentary following the guidance point includes these

favorable public health consequences, among others, of involving the community: equity in decisions regarding level of care and treatment and its duration, and equity in plans for releasing results and distributing safe and efficacious HIV prevention products. These would truly be favorable consequences, if a meaningful participatory process can, in fact, take place. However, the recognition that other stakeholders will also be involved, ones with more power and authority than the community, prompts initial skepticism about the ability of community members to wield significant influence in the decision-making process. We can only hope that such skepticism eventually proves to be mistaken.

It is the case for this recommendation on community engagement as for the other guidance points that prompt difficult questions: answers are forthcoming only in the context of planning and conducting a microbicide trial. Communities are not homogeneous or monolithic. What if some members want a microbicide trial but others do not? What if community members or groups differ in what they consider fair benefits following a trial that yields a successful microbicide? Clearly, what is needed here is a fair process for reaching decisions when agreement is lacking on the substantive ethical issues.

According to one useful account, procedural fairness requires that the process of decision making be transparent, inclusive, impartial, ensure due process and be accountable (Daniels and Sabin, 1998). The rationales for decisions should be publicly accessible (transparent); those involved in the decision-making process at all levels should include a wide range of individuals and groups (inclusive); the process should ensure avoidance of conflict of interest (impartial); it should include a mechanism for challenge and revision of plans, including the opportunity for revising decisions (due process); and have some form of accountable regulation of the decision-making process (accountable).

The commentary under Guidance Point 2 in the UNAIDS/WHO document cites a telling reason for involving the community: 'Failure to properly and genuinely engage communities early in the stages of research planning may result in an inability to properly conduct and complete important trials.' Evidence that this is not just idle speculation comes from two episodes that prevented an HIV pre-exposure prophylaxis (PrEP) trial from coming to fruition. The Global Campaign for Microbicides issued two reports that describe the episodes, which occurred in Cambodia and Cameroon, and suggested some lessons for the future (Global Campaign for Microbicides, 2009b,c). The episode in Cambodia is recounted below.

The Cambodian Tenofovir Trial

The subjects in the Cambodian study were sex workers, a group always at high risk of HIV infection. The method to be studied to see whether it could prevent HIV infection was tenofovir, an antiretroviral medication used as part of the cocktail for treatment of patients with HIV/AIDS. The Cambodian study, launched in 2004, was one of several that began that year to study the safety and efficacy of tenofovir compared with placebo. Among the important players in this drama was a non-governmental organization (NGO), a union of Cambodian sex workers called The Women's Network for Unity (WNU). The GCM report provides details of the political climate and other background circumstances that led to the eventual stopping of the trial. One of the key concerns of the sex worker community was whether members of that community would ever receive the benefits of HIV prevention if tenofovir turned out to be effective. WNU held a press conference in 2004 in which it made the following statement: '[i]f our members agree to take the risk, which may one day benefit people in richer countries and the drug company, then we deserve adequate protection for our future lives and our families. The high cost of this drug means that even if it is successful in preventing HIV/AIDS, Cambodian sex workers will most likely never be able to afford it' (p. 16).

The research team then took steps to address this concern and succeeded in making an agreement with the manufacturer of tenofovir, Gilead Sciences, stating that trial participants would receive free tenofovir for two years after the study if it proved successful. However, misunderstandings and mistrust ensued. Based on other information it received, the community doubted both whether the company would honor the agreement, and also whether the community had received accurate information about the safety of tenofovir. As communications between researchers and the WNU about the side effects of tenofovir continued, it did not improve understanding but rather increased mistrust on the part of the community. After learning that tests of safety of drugs in industrialized countries are done first in animals, sex workers responded by saying 'we are not monkeys or guinea pigs'. Eventually, the sex workers demanded medical insurance to cover any adverse effects of the medication, including trial-related injuries after their participation ended, but this was disallowed by the US National Institutes of Health, one of the sponsors. As the situation deteriorated further, large public

protests ensued, the Prime Minister of Cambodia became involved in the protest, and in mid-August of 2004, the Cambodia tenofovir trial came to a halt. In recounting this fascinating tale, the GCM report concludes by saying that ‘...beyond practicality, political expediency, and research security—the obligation of researchers to engage effectively with the trial participants and host communities is a human rights issue’ (p. 29). It will require further analysis to determine just which human rights are at stake here and whether human rights were actually violated, or whether a series of poor communications and inadequate disclosure of information to participants and the community produced a justifiable mistrust of the researchers and sponsors.

It is evident from the GCM’s detailed report that some blame for the unfortunate outcome is shared by the several parties involved. Nevertheless, the story provides a cautionary tale regarding the importance of forging ties with the community, fostering transparency in all communications, and working more cooperatively together to reach a goal to which all parties aspire: finding an effective method of prevention against HIV infection.

Toward a More Hopeful Future

Despite the past setbacks, hope remains for success in finding an effective HIV-preventive microbicide. Research is moving forward on other HIV biomedical preventive methods at the same time. The results of a vaccine regimen tested in Thailand and reported in late 2009 showed some promise, but too little efficacy to gain approval from a regulatory agency. In July 2010, results of a vaginal microbicide trial in KwaZulu-Natal, South Africa, showed moderate though unmistakable efficacy of the product. There are also several ongoing PrEP trials, one of which involves the drug, tenofovir, the same product used in the Cambodian clinical trial. If a future microbicide or one of the other preventive methods demonstrates sufficient efficacy, the ethical challenges discussed in this article will see the light of day. Adherence to the ethical recommendations in the UNAIDS/WHO guidance document will help to ensure that the goals of research and public health are achieved simultaneously.

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