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Informing Research on HIV Prevention: A Consultation

Sharon Fonn

C. Elizabeth McGrory
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By
Sharon Fonn
C. Elizabeth McGrory

Population Council

The Population Council is an international, nonprofit, nongovernmental institution that seeks to improve the wellbeing and reproductive health of current and future generations around the world and to help achieve a humane, equitable, and sustainable balance between people and resources. The Council conducts biomedical, social science, and public health research and helps build research capacities in developing countries. **C. Elizabeth McGrory, ScM**, is Staff Program Associate, International Programs Division, Population Council.

The Women's Health Project (WHP), Department of Community Health, University of Witwatersrand, South Africa, is an independently funded national NGO comprising research, training, networking, and advocacy and consultancy divisions. WHP is working towards a situation where a political, economic, and social environment, and an infrastructure and institutions exist to satisfy women's needs such that all women enjoy their optimal level of health. **Sharon Fonn, MBBCh PhD FFCH**, is Deputy Director of the Women's Health Project.

For information or additional copies:
Population Council
One Dag Hammarskjold Plaza
New York, NY 10017 USA
Telephone: (212) 339-0500
Fax: 212-755-6052
E-mail: pubinfo@popcouncil.org
www.popcouncil.org

Women's Health Project
Department of Community Health
University of Witwatersrand
P.O. Box 1038
Johannesburg 2000, SOUTH AFRICA
Telephone: 27 11 489 9917/9905
Fax: 27 11 489 9922
E-mail: womenhp@sn.apc.org

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INTRODUCTION

According to a 1998 report by UNAIDS/WHO, HIV infection among women is the fastest-growing segment of the AIDS pandemic, especially in developing countries. Of the estimated 16,000 daily new HIV infections, 90% are in developing countries and over 40% are in women. Unfortunately, the three HIV-prevention strategies put forward by the public health community—monogamy, condom use, and treatment of sexually transmitted infections—are not feasible for many women. Imbalance in the power relations between men and women puts women at particular risk. Women, who may rely heavily on their partners for economic survival, cannot typically abstain from sexual contact, and while they themselves may be monogamous, their partners may not be. Many women have a difficult time negotiating condom use, particularly in the context of primary partnerships. Female condoms, while promising, also require partner cooperation, are not widely available, and remain relatively expensive. Finally, diagnosis and treatment for sexually transmitted diseases is simply not available to many women; moreover, many sexually transmitted infections are asymptomatic in women. Women urgently need a means within their personal control to protect themselves against HIV. Recognising this need, a number of international and non-governmental organisations and government agencies have called for the development of microbicides, products that women could use vaginally to prevent infection with sexually transmitted infections (STIs), particularly HIV.

The Population Council is one of the organisations currently working to develop a vaginal microbicide. The Council's lead compound, called PC-515, has already been tested in animals and has also undergone initial testing for safety and acceptability in a small number of women. The Council is now planning a more in-depth and complex expanded safety and acceptability trial. Through a process of research and consultation the Council identified South Africa as an ideal site for these trials due to its

excellent research infrastructure and high incidence of HIV among heterosexual women. There are, however, significant ethical considerations in this kind of research: the products, funding, and researchers largely come from outside South Africa and from first-world countries; the trial is scientifically complex; the topic raises sensitive personal, social, and economic issues; and the trial concerns a stigmatised and fatal disease.

In order to inform the proposed research in South Africa, and further explore the ethical issues involved, the Population Council wanted to consult with appropriate government, research, activist, and community groups. To complement its ongoing collaboration with researchers and government agencies, the Council co-sponsored a consultative meeting with the Women's Health Project to broaden and continue the process. The meeting was also intended to inform a range of interested parties in South Africa about microbicides research and the prospects of microbicides in the fight against HIV/AIDS. This report summarizes some of the most pertinent background information, highlights some of the issues that emerged and were discussed during the consultation, and identifies the recommendations made for proceeding with the research.

THE CONSULTATION

The consultation was a partnership between the Population Council and the Women's Health Project in Johannesburg, and each brought complementary strengths to this process. The Council is a non-profit, international research organisation, based in New York, USA, with offices in nearly 20 countries around the world. Since 1952 it has conducted research in social science, public health, reproductive biology and health, and contraceptive development. The Council's work in microbicides started in the late 1980s and grew out of work on reproductive health and a gender analysis of the growing global HIV/AIDS problem that underscored the lack of options for women to protect themselves from infection. The work on microbicides continues to be informed by this broad

perspective. The Council is one of several organisations that have played a key role over the last decade in advancing the field of microbicides with a comprehensive program that includes: laboratory research to develop and screen compounds; clinical testing to evaluate safety and effectiveness; social science research on relevant issues; public awareness and policy education; and ongoing consultation with other scientists and industry partners, and with women's health advocates and people in communities where clinical trials are being planned.

The Women's Health Project (WHP) is a national non-governmental organisation started in 1991, when it initiated policy-oriented research to ensure that women's health issues were taken into account in the transition to a democratic South Africa. The organisation combines technical research skills, expertise in health, and health service development with an advocacy and training section. The WHP plays a key role in South Africa in ensuring that policy and health service development are informed by grassroots needs. The work of the WHP is central to the development of health and development policy and policy implementation in South Africa, and has contributed significantly to the international arena of women's health and gender through participation in numerous international networks and endeavours.

The Council and the Women's Health Project jointly planned and hosted this consultation, which brought together nearly 70 activists, researchers, and government officials for two intensive days of presentations, discussion, and debate. The joint commitment of the two organisations to broad consultation made for a good partnership. WHP's overarching commitment to "including the voice of everyday women" is manifest in all its areas of activity: research, education and training, and policy development and advocacy. Consistent with its primary objective of making a positive contribution to women's lives, the WHP and its constituency would welcome a safe, acceptable, and effective vaginal microbicide. The organisation has developed specialised expertise in defining and refining

the complex technical, political, and social aspects of health and disease, and brought to the meeting its capacity for making technical knowledge easily understandable. This greatly facilitated frank, open, and productive discussion across backgrounds, disciplines, and interest groups.

OBJECTIVES

As partners in planning and convening the consultative meeting, the WHP and the Population Council saw the need for a meeting that would provide a forum for dialogue, where all interest groups could find out more about microbicides and microbicides research, voice their opinions and concerns about the study, and offer suggestions. Thus the meeting had several related objectives:

- to inform a range of interested parties in South Africa about microbicides research and the prospects of microbicides in the fight against HIV/AIDS
- to discuss implementation of the Population Council's Phase II microbicide clinical trial in South Africa
- to develop concrete recommendations for carrying the study forward in the most socially responsible and ethical way

PARTICIPANTS

Because of its position in the health community, the WHP identified a wide range of stakeholders who could contribute to and learn from the dialogue, inform the study, and help define its parameters. The meeting included individuals with different skills and perspectives, from a variety of disciplines and backgrounds. Participants included activists, government health officials, academics, researchers, ethicists, representatives of NGOs working on AIDS/HIV, and people from community organisations.*

*See Appendix for list of participants.

This diversity greatly enriched the discussion and the kinds of suggestions that emerged.

PROCESS

To develop a common understanding about some of the key issues related to microbicide development and testing, all participants were sent background reading material about the scientific and ethical aspects of vaginal microbicides research before the meeting. A half-day programme was organised immediately before the main meeting for participants who were unfamiliar with some of the technical terminology and concepts of clinical trials generally. Research methods were described and discussed to underscore the importance of, for example, randomised controlled trials and the key requirements for an expanded safety trial such as the one the Council is planning. Participants quickly grasped the salient points and articulated many of the complex and challenging ethical issues, and freely asked questions and made suggestions. Council staff learned a great deal about the social context of the study and the situation in South African communities. Many of these issues continued to be discussed and debated throughout the following days.

The full meeting included an intensive two-day programme of presentations and discussions. To take full advantage of the richness and diversity of participants' experiences and views, the entire meeting was held in plenary session. The programme included presentations, discussions, and recommendations on:

- microbicides: what they are, how they work, and what we still need to know
- the Population Council's work on microbicides and plans for work in South Africa
- the factors that contribute to South African women's risk of HIV infection and the place of women-controlled methods in addressing this risk

- ethical challenges of microbicides testing
- guidelines for ethical research
- informed consent, standard of care, and recommendations

MICROBICIDES: AN OVERVIEW

Although no proven microbicides are yet available anywhere in the world, a number of researchers and research organisations are working on a range of approaches to find a safe and effective product. There are several ways a potential microbicide could work: killing the virus; blocking viral adhesion; preventing viral uptake; stopping viral replication; or stimulating the local immune system. A microbicide could potentially take the form of a gel, foam, film, suppository, or cream, formulations similar to those used in currently available spermicides. In most leads currently being pursued, women would insert the microbicide into the vagina before sexual intercourse. Microbicides should be widely available, stable in a range of climates, and affordable to even the world's poorest women. Ideally, microbicides should be available in both contraceptive and non-contraceptive formulations. This choice will benefit both women who choose not to have children and women who choose to have children, whether their decision is based on their personal desires or on considerations of their economic well-being or social status.

One of the major challenges in microbicides research, and in HIV/AIDS-prevention research more generally, is that the exact biology of HIV transmission is still not known. For example, it is not known whether it is the cervical or vaginal cells in the female reproductive tract that are more susceptible to HIV infection, or by which exact mechanism the viral elements enter the human cell. This has hampered the search for new microbicide compounds since scientists do not know precisely where to target their efforts.

Most clinical trials of microbicides currently underway are investigating the microbicidal properties and potential of existing vaginal or

other topical products. This approach has a number of advantages over entirely new product research. Many of these existing products are already licensed and available over the counter; they have been used over a period of time, which suggests that they are generally safe in typical use; and answers about their effectiveness as actually used can be determined more quickly.

Nonoxynol-9 (N-9), the active ingredient in most currently available spermicides, has been in use for decades and is one of the substances being actively investigated as a microbicide. In the laboratory it kills a wide variety of STI pathogens, including HIV. In animal studies N-9 has been shown to block SIV in macaque monkeys. In clinical trials it has been shown to reduce sexual transmission of gonorrhoea and chlamydia. However, a recent study among sex workers in Cameroon did not demonstrate any greater effectiveness of N-9 film compared with a placebo in reducing transmission of HIV infection. This may be due to the formulation (the film may not have had sufficient time to melt and become active) and other trials are underway testing an N-9 gel product. Hopefully, a conclusive answer about the potential of N-9 as a vaginal microbicide will soon be available.

THE COUNCIL'S WORK ON MICROBICIDES

One of the approaches researchers are taking to developing new microbicides is investigating ways of preventing HIV and STI infection by coating the inside of the vagina with a substance that blocks viruses and possibly other pathogens. The Council's PC-515 would function in this way: it is a sulfated polymer, which has shown promising test results in the laboratory and in animals. The active ingredient of PC-515 is lambda carrageenan, which is derived from seaweed. Carrageenan forms a natural gel and is commonly used as a thickener in foods (such as ice cream and baby formula) and as an emulsifier in topical creams and lotions. Regulatory authorities consider it safe for consumption and topical appli-

cation. It has a number of other properties that make it attractive as a microbicide: it is inexpensive, stable, and forms a natural gel when mixed with water. Laboratory tests show that PC-515 blocks HIV in test tubes, and similar enveloped viruses in animals.

After extensive laboratory and animal testing, the first phase of clinical testing, to determine basic safety and acceptability, was completed in April 1998. In this Phase I study, conducted in the United States, Dominican Republic, Chile, Thailand, and Australia, 35 women applied the product once a day for seven days. The women abstained from sexual intercourse during the study. Results indicated that the product caused no significant signs of irritation and that the women generally found it acceptable and easy to use, though some found it to be too messy.

The next step in clinical testing is to further establish safety in conditions that more closely mirror "real life" by including a larger number of sexually active women, and having them use the product for a longer period of time (approximately one year). If the Phase II trial indicates that the product is safe, a much larger, longer, and far more complex Phase III study will be conducted to determine whether the compound actually works to prevent infection with HIV and other STIs. In order to measure effectiveness in a manner that is feasible in terms of time, logistics, and resources, the Phase III trial must be conducted in locations with a large, stable population of women with high incidence of HIV caused primarily by transmission during vaginal intercourse, and with good laboratory facilities and research infrastructure. South Africa generally, and the proposed sites for this study in particular, fit these criteria well. The proposed study is therefore intended to provide further evidence of safety and acceptability of PC-515, and also to help determine whether the larger, more complex Phase III effectiveness trial is feasible in these sites.

Objectives of the Phase II Trial of PC-515

The Council's proposed Phase II expanded safety and acceptability trial is a randomized, placebo-controlled, double-blind trial designed to further

assess the safety of PC-515. It will be conducted by the Population Council in conjunction with the Medical Research Council's Centre for Epidemiological Research in Southern Africa, the University of Cape Town, and the Medical University of Southern Africa. The project sites are family planning and general health clinics in two locations—Ga-Rankuwa near Pretoria and Gugulethu in Cape Town. The trial is the first large-scale microbicides trial to be done in a population of women who are not sex workers and with a microbicide formulation that is non-contraceptive. In the trial, approximately 300 women will use the gel or placebo for approximately one year (300 woman years total) by applying it vaginally at least three times weekly as well as before intercourse (no matter how often that occurs). The Phase II trial has several objectives:

- to further assess the safety of PC-515
- to gauge the acceptability of the gel
- to investigate the feasibility of conducting a microbicides trial among women who are not sex workers
- to understand women's reactions to a candidate microbicide that is not a contraceptive
- to explore the dynamics of microbicide use in a population where the practice of dry sex and the use of a range of products to achieve this is reported to be common
- to gather preliminary data about effectiveness against HIV and other STIs

The researchers plan a short pilot study with ten women in each site to ensure that the procedures work well.

After enrolling in the trial women will come to the clinic monthly to be examined for signs of irritation and tested for sexually transmitted infections; every three months they will be tested for HIV and asked a series of acceptability questions. At these visits the women will receive safer-sex counseling, free condoms, and counseling to ensure that they understand the trial requirements and objectives and consent to be in the

Which Women Are Eligible for the Trial?

To participate in the Council's Phase II trial, women must be:

- in good health (as determined by medical history, examination, and laboratory tests)
- 18 years old or older
- resident in the area for at least one year, with no intention of leaving for another year
- HIV-negative when they enroll
- not pregnant or intending to become pregnant in the next year
- willing and able to comply with all the procedures involved
- able to give informed consent

trial. Prior to being tested for HIV and receiving their results (if they choose, women have the option not to get their results) they will engage in pre- and post-test counseling. If a woman is found to have a treatable STI she will receive treatment; if she is found to have HIV or another condition she will be referred to health and support services available in the community.

SOUTH AFRICAN WOMEN AND HIV

In the context of the global AIDS epidemic, sub-Saharan Africa is hit particularly hard: this region is home to approximately two-thirds of the people living with HIV in the world. Sub-Saharan Africa is also the area with the fastest rate of increase in new HIV infections, and the primary route of HIV transmission throughout Africa is heterosexual intercourse. In the African pandemic, women are particularly affected: four out of five women in the world infected with HIV live in Africa.

South Africa has been especially affected by the HIV epidemic; prevalence data from 1997 indicated that approximately 16% of the population was infected, with rates much higher among some groups. In

some provinces incidence doubled between 1996 and 1997 and it exceeds 10% per year in some parts of the country. As in the rest of the region, women are most at risk of HIV infection, conditioned by physiological, social, sexual, and economic factors. All of these issues contribute to the complexity and urgency of microbicides trials.

Physiological Factors

Physiologically, women's risk of HIV infection from unprotected sex is at least twice that of men. As the protective cells of young women's vaginas are not well developed, they are at even greater risk than mature women. The rate of HIV infection in pregnant women is increasing: women between the ages of 14 and 25 seem to be at the highest risk. Some cultural and social practices may increase women's risk of being infected with HIV: many women in South Africa use a range of products in the vagina to satisfy men's desires for dry, tight sex. The substances can cause inflammation, lesions, and erosion of the vaginal walls which may make it easier for HIV to enter. Anal intercourse also carries high risks of HIV transmission and is practiced by heterosexuals to preserve virginity, to protect against pregnancy, or for sexual pleasure. There is some evidence that, in the face of the AIDS epidemic, anal sex is also mistakenly being used as a safer-sex strategy.

Socio-economic Factors

In spite of strong protections in South Africa's new Constitution, historically the majority of South African women have had little or no control over their sexuality or reproductive health. While men are encouraged to experiment with multiple partners before marriage, women are pressured to remain virgins until they marry. After marriage, women are generally expected to be available sexually to their husbands, and may be unable to challenge their husbands' extra-marital affairs or insist on condom use even when they know they are at risk. South Africa's history of migrant labour, where men spend long periods away from their wives and may have multiple sexual partners (including sex workers), puts women at

even greater risk. In addition, some women are in polygamous marriages, where if anyone in the group is infected, everyone is at risk.

The HIV/AIDS epidemic also has major implications for women's central role as caregivers in their families. Because of the social expectation that women will be the primary caregivers and will stay at home, they may not be encouraged or educated to develop labour market skills. Resulting financial dependence on their partners is central to their unequal status and further entrenches their risk of HIV. For example, if a woman leaves her partner because he refuses to use a condom, she may lose her home, access to food and shelter, and even her children and extended family. Women's economic vulnerability may also lead them to engage in sex work, a thriving industry in South Africa. Women's roles as primary caregivers also mean that once someone in the family has AIDS and is ill, women are generally expected to take care of the sick person. Finally, when a parent dies of AIDS and children are left as orphans in child-headed households, girls are likely to carry the greatest burden of looking after the family.

Sexual violence also puts women at risk of HIV. The incidence of rape in South Africa is among the world's highest, with an estimated 370,000 women raped every year. This is an increasing and alarming source of women's vulnerability to HIV.

During discussions, participants underscored the enormous amount of work that needs to be done in the field of HIV/AIDS prevention in South Africa. There was consensus among the participants that given South African women's great risk of HIV infection, interventions that would help increase awareness and give women greater control in protecting themselves from infection should be encouraged. Several participants noted that the considerations related to conducting a clinical trial for microbicides should be seen in the context of this urgency.

The research team's considerable challenge is to design a safety trial that is both scientifically rigorous and ethically sound. Issues of ethical

clinical testing for microbicides have been debated in a variety of fora for several years. The Council and others have worked to develop consensus around research models that meet both clinical and ethical criteria. Since the Population Council identified the sites in South Africa for this research, it has been engaged in ongoing consultation with members of the women's health community, the Ministry of Health in South Africa, microbicides experts in South Africa and abroad, and with the local principal investigators and staff to apply these standards to the Phase II trial being planned.

ETHICAL FACTORS AND IMPLICATIONS FOR RESEARCH DESIGN

In the area of human research, there are three basic accepted rules of ethics:

- **autonomy:** that participants are in no way forced or coerced to participate in research, and that they agree to do so freely after thorough informed consent
- **beneficence:** that the research will do more good than harm
- **justice:** that those taking the risks of participating in research risks must share in its benefits

These general principles provided a useful framework for the meeting participants to discuss and debate various aspects of the planned clinical trial. With the combined clinical and social science expertise of the research team, many of the pressing ethical issues had already been carefully considered prior to the consultation. However, the researchers actively encouraged input from the health activists, community-based organisations, and policymakers at the meeting to help design and implement the study in South Africa as ethically and sensitively as possible. To this end, participants discussed and debated a number of issues related to the researchers' responsibilities before, during, and after the trial. Participants explored a range of challenging questions, including the following:

- What health and support services should be provided during and after the trial?
- What are the implications of providing these services for ensuring voluntary participation?
- What would happen to study participants who choose to leave the trial?
- What would happen to study participants who became HIV-positive during the trial?
- What informed consent process would ensure that trial participants truly understand the trial?
- How can the researchers balance community participation and openness with ensuring the privacy of the trial participants?
- What are the researchers' responsibilities as advocates?
- What are the researchers' responsibilities related to building a better-functioning health system, if, for example, the referral system does not work effectively?
- How can the researchers anticipate and address the potential power imbalances between themselves and the research participants?

The discussions returned repeatedly to issues of autonomy and voluntary participation, especially as manifest in the informed consent process and the services provided as part of the trial. There was a great deal of discussion about how to ensure that the decision to participate in a trial is and remains truly voluntary. A challenge in all research is to provide fair compensation for participating in a trial without crossing the line to providing enough money or services that they could serve to effectively coerce people into participating. These issues are particularly sensitive in areas with high levels of poverty and unemployment and where access to some types of services can be limited. The researchers at all the sites had already given careful consideration to these questions, and had consulted extensively with others about what would be reasonable to pro-

vide: modest monetary compensation for time and transportation for each visit; refreshments; screening and treatment for STIs; and safer-sex counseling and condoms. Several aspects of this were discussed: reimbursement for time and travel costs; the services provided to trial participants; and less tangible issues such as power dynamics.

REIMBURSEMENT

The issue of monetary reimbursement raises complex ethical issues for researchers and for trial participants. On the one hand, people may be desperate for money and may agree to participate in research that they are not

Participants' Responsibilities During the Trial

During the trial, participants will agree to:

- visit the clinic every four weeks
- insert one dose of PC-515 (or the placebo) three times a week, regardless of sexual activity
- insert one dose of PC-515 (or the placebo) no more than one hour before having sex, each time they have sex (there is no maximum limit)
- participate in safer-sex counseling and condom promotion at each clinic visit
- be tested for HIV (every three months) and other STIs (every month) through vaginal swabs and blood drawing:
  - they will receive treatment for any STIs diagnosed
  - they may refer their partners for a medical consultation for STIs if they choose
  - they will be referred to services in the community if they are HIV-positive
- answer questions about acceptability such as the texture, smell, taste; whether they would use the gel again; whether they would recommend it; what their partners think; how they perceive the applicator; reasons for dropping out of the trial

fully comfortable with. On the other hand, people who view their participation in the trial primarily as a way of earning money might not be sufficiently motivated to comply with a complicated protocol. Payment can also be interpreted as "danger pay," implying more risk than actually exists.

The participants at the meeting recommended that people's costs must be acknowledged, seriously evaluated, and discussed with research participants. The participants felt strongly that the originally proposed reimbursement for clinic visits was not adequate, and noted that although the women in the trial may agree to this amount, women are often conditioned to undervalue their own time. Several participants cautioned that the level of reimbursement should be consistent with that provided in other similar studies so as not to implicitly undervalue women's time as compared with men's. Participants advised that the researchers engage in detailed discussion about this with women in the communities who are potential trial participants. Following the meeting, the amount was adjusted in the study protocol and budget.

SERVICES

One of the major "researchers' dilemmas" in microbicides effectiveness testing is that it needs to be conducted among women at some risk of contracting HIV; exposure to HIV is necessary to evaluate whether the microbicide works. At the same time it is well known that HIV can be prevented through correct and consistent condom use. This presents the researcher with a real dilemma—on the one hand needing HIV transmission to occur to test a product's effectiveness, and, on the other, the ethical obligation to actively encourage condom use among study participants even though it may dilute the study's ability to determine whether a product works. This dilemma also has implications for study findings—as any future effectiveness trial will really only answer the question of how well the product works over and above condoms, rather than on its own, as most women might likely use a microbicide.

There is general consensus among microbicides researchers that active counseling in safer-sex practices and condom promotion are critical components of an ethical microbicides trial. As conceived, the trial provides safer-sex counseling and active promotion and free supply of condoms for all trial participants. Because the study requires HIV testing, the protocol also calls for intensive counseling before HIV testing and after HIV status is assessed. HIV results will remain confidential and women participating in the trial will also be able to choose whether or not to know the results of their HIV tests. Because of the stigma associated with being HIV-positive, women in the trial can decide whether or not to inform anyone about their status. Women diagnosed as HIV-positive can continue to participate in the trial if they choose, so that leaving the trial does not signal HIV serostatus. The researchers are working with consultants and local groups at the study sites to develop appropriate and comprehensive counseling interventions for safer sex, HIV testing, and, if women choose, disclosure of HIV status.

In addition to these counseling services, women in the trial will be screened through laboratory tests for a variety of sexually transmitted infections (STIs), and will be treated for any that are diagnosed. While the treatment offered will not differ from standard practice at the clinics, the trial will include laboratory testing for these STIs which is not generally available in the clinics where the trial will take place. Women who test positive for HIV either at screening or during the course of the trial will be referred to existing health and support services in the community. Similar referrals will be made for other conditions identified during the study. Although women in the trial will receive good medical care and counseling and free condoms, potential trial participants need to understand that the main benefit of their participation in this trial will be to help other women later on if the product proves to be effective.

The trial will build on, and draw on, services already available in the community, for several reasons. First, it is hoped that this approach will

contribute to strengthening available health services in a way that is sustainable. Second, providing much better services than those available in the community could severely undermine the concept of voluntary participation by serving as undue inducement for women to enroll in the trial. Further, if the protocol calls for such services to be withdrawn if a person leaves the trial, it could prevent people from withdrawing even if they want to for other reasons. The ethical imperative of voluntary participation also dictates that participants will be encouraged to stay in the trial even if they seroconvert or stop using the study product.

Meeting participants underscored the following areas where the study teams and staff should pay particular attention to best meet trial participants' needs:

- training women to be assertive (e.g., about condom use)
- informing women about support and services available for problems that could arise during the trial (such as rape)
- offering general information to women about their bodies
- facilitating contact between trial participants as resources and for mutual support
- facilitating access to support organisations and counseling for women who are HIV-positive at the initial screening or who seroconvert during the trial
- ensuring that women receive good-quality, non-judgmental counseling
- encouraging women to know their HIV status, while respecting that the individual has the final choice
- allowing women to stay in the trial regardless of whether they comply with the protocol
- reporting back to the communities once the trial is finished, via newsletters and community radio shows

ENSURING INFORMED CONSENT

Participants were unanimous in their view that ensuring true informed consent is vital to an ethical study. A great deal of the discussion centered on how to ensure that the research participants gain a thorough understanding of the study objectives, what will be expected of them, and any potential risks. The researchers underscored their commitment to actively explore ways to best ensure that informed consent in this study is truly informed and participation truly voluntary. Several key issues were explored in the discussion.

Language and Concepts

In order to ensure that trial participants have given truly informed consent it is critical to provide sufficient information about the study: objectives, procedures, risks, and benefits. Given that this study is quite complicated, it can be challenging to come up with terminology and methods of communication to convey some of the trial's key concepts in a manner that is understandable and accurate. This problem is compounded by language difficulties: several participants stressed that many of the local languages in South Africa do not contain terms for concepts used in the study. In some cases terms do exist but are pejorative, for example, about certain sexual practices. The research team was referred to existing materials that had been developed to address these concerns. It will be critical to test translations of key concepts and terminology for both accuracy and nuances to ensure that the information is presented in a way that is comprehensive, understandable, and non-judgmental.

Process

Meeting participants also underscored that informed consent should not be viewed as an "event" of signing a piece of paper, but an ongoing and multi-step process throughout recruitment, screening, enrollment, and the course of the study. The study staff will need to explain the study in detail and develop a rigorous process to probe for women's understanding. It will

be critical to develop a rapport that will facilitate women's ability to ask questions. Several people suggested that other approaches, such as booklets and videos, be explored. Finally, one participant at the meeting suggested that after the woman had been informed and counseled about the study, both she and the counselor should sign the informed consent form as this would signify a mutual commitment to the study and to one another.

Community Participation

Questions were raised about what level of community involvement is appropriate in "consenting" to research, beyond the consent of the individual research participants. What organisations and other individuals should be informed and consulted about the study? Who exactly would be involved in giving informed consent? There was strong consensus that informed consent should come solely from the individuals involved after a careful and detailed process of recruitment, education, and counseling about the study.

The researchers described some of their ideas for community involvement and information sharing. Meeting participants debated whether advisory committees representing the wider community should be formed and how community leaders should be consulted. While everyone agreed that community participation and transparency is desirable and indeed necessary to the research process, some participants expressed strong concern that such consultative processes could impede the progress of the research, and could also potentially compromise the confidentiality and privacy of the women. These participants underscored the urgency of the HIV/AIDS problem for women in South Africa and cautioned against the research getting too "bogged down" in community consultation and politics. There was finally general consensus that the trial participants constitute the primary community for the trial, and that they should be asked to guide the researchers about the appropriate level and extent of community involvement. Participants strongly urged the researchers to explore this with women enrolled in the pilot study.

Power

Finally, researchers must be aware of the power differentials that condition the relationship between researcher and trial participants. Women may feel pressured to stay in the trial to "please" the researchers or because of the perceived power of the researchers. This means that the researchers are compelled to remind women at each visit of their absolute autonomy—that it is always the woman's decision whether to participate in the study and they can withdraw from the trial at any time without consequences.

LOOKING AHEAD

In many of the discussions, participants' very useful recommendations and ideas were accompanied by the implicit or explicit recommendation that the consultative process continue to the next level—at the study sites and with participants. For a number of issues, including compensation, informed consent, and appropriate community consultation there was a strong sense that answers should be arrived at with the women in the communities where the trials will take place. A number of people at the meeting felt that this would break new ground, making ethical debates and commitment to participation meaningful.

Meeting participants felt strongly that the process of the consultation itself and the level of discussion confirmed that lay people can understand, debate, and address these complex concepts. Participants quickly understood the issues related to the trial, and raised and discussed many of the complex ethical, biological, and research challenges the researchers face. The discussion during the meeting and the participants' observations underscored that individuals will appropriately weigh the risks and benefits of participation and make their own decisions based on the realities of their lives and their own interests.

The presentations and discussions highlighted many of the responsibilities and challenges that face researchers working to conduct microbicides trials in the most ethical manner. Apart from ensuring the technical

and clinical integrity of the research, researchers also have to be committed to the parallel processes of informed consent, counseling and education, community participation, and empowerment. For education and counseling to be effective, researchers and study staff have to be willing to build relationships with the research subjects. They have to be consistent and clear about the standard of care they plan to provide. They have to be aware of what health and support services are available in the community to help women who test HIV-positive or face other problems. At its best, the research process holds potential for contributing to empowering women with a greater sense of their autonomy and control over their health and lives. We are all compelled to do at least this while we urgently seek a better way for women to protect themselves from HIV.

APPENDIX: PARTICIPANTS

Sylvia Abrahams
Western Cape, Department of Health
Reproductive Health
Private Bag X19
Bellville 7535 South Africa
Tel: 021 948 9050
Fax: 021 949 9611

Christina Adonis
North-West Province, Department of Health
Private Bag X2068
Mmabatho 2735 South Africa
Tel: 0140 87 5228
Fax: 0140 87 5332
Cel: 082 578 1145

Ivy Appollis
National AIDS Convention of South Africa (NACOSA)
P O Box 1773
Port Elizabeth 6000 South Africa
Tel: 041 711780
Fax: 041 5061486

Linda-Gail Bekker
University of Cape Town Medical School
Room 231, Third-Year Bldg., Observatory
Cape Town 7925 South Africa
Tel: 021 406 6364
Fax: 021 461 1471

Kelvin Billinghurst
Mpumalanga, Department of Health
Private Bag X11285
Nelspruit 1200 South Africa
Tel: 01375 28085
Fax: 01375 51133

Kelly Blanchard
Population Council
One Dag Hammarskjold Plaza
New York, NY 10017 USA
Tel: 212 339 0656
Fax: 212 755 6052

Emelda Boikanyo
Consultant, Midwife
P O Box 14764
Lyttleton 0140 South Africa
Tel: 083 755 2153
Fax: 012 702 1464

David Coetzee
Department of Health–STD Program
Private Bag X828
Pretoria 0001 South Africa
Tel: 012 312 0129

Nicol Coetzee
Department of Community Health
University of Cape Town Medical School
Anzio Road, Observatory
Cape Town 7925 South Africa
Tel: 021 406 6300
Direct: 021 406 6486
Fax: 021 406 6123

Daphney Conco
Women's Health Project
P O Box 1038
Johannesburg 2000 South Africa
Tel: 27 11 489 9918
Cel: 083 449 8611
Fax: 27 11 489 9922

Glenda Daniels
The Star
P O Box 1014
Johannesburg 2000 South Africa
Tel: 011 633 9111/2317
Fax: 011 834 3935

Liz Dartnell
Centre for Health Policy
P O Box 1038
Johannesburg 2000 South Africa
Tel: 011 489 9938

Mary De Haas
Department of Social Anthropology
University of Natal
P O Box 18091
Dalbridge 4014 South Africa
Tel: 031 260 2431
Fax: 031 260 2829

Christopher Elias
Population Council
P O Box 138
Pratunam Post Office
Bangkok 10409 Thailand
Tel: 66 2 251 4766
Fax: 66 2 255 5513

Charlotte Ellertson
Population Council
Apartado Postal 105-152
11560 Mexico, D.F., Mexico
Tel: 52 5 659 8541
Fax: 52 5 554 1226

Clive Evian
AIDS Management & Support
P O Box 92022
Norwood 2117 South Africa
Tel: 011 786 6492
Cel: 082 456 3717
Fax: 011 786 6492

Sharon Fonn
Women's Health Project
P O Box 1038
Johannesburg 2000 South Africa
Tel: 27 11 489 9914
Fax: 27 11 489 9922

Barbara Friedland
Population Council
One Dag Hammarskjold Plaza
New York, NY 10017 USA
Tel: 212-339-0629
Fax: 212-755-6052

Katherine Garson
Rapporteur
Tel: 011 447 1730

Fatima Hassan
Centre for Applied Legal Studies
(CALS) AIDS Law Project
Private Bag X3
WITS 2050 South Africa
Tel: 011 403 6918
Fax: 011 403 6930

Anwar Hoosen
Medical University of
Southern Africa
Department of Medical Microbiology
P O Box 211
Medunsa 0204 South Africa
Tel: 012 521 5667
Fax: 012 521 5727

Carel IJsselmuiden
Department of Community Health
University of Pretoria
P O Box 667
Pretoria 0001 South Africa
Tel: 012 339 8618/8608
Fax: 012 323 8534

V. Isaacs
Western Cape, Department
of Health
Programme Development
Private Bag X19
Bellville 7535 South Africa
Tel: 021 948 9050
Fax: 021 949 9611

Marge Jobson
Human Rights Institute of South
Africa (HURISA)
P O Box 784678
Sandton 2146 South Africa
Tel: 011 884 2647
Fax: 011 884 0421

Christina Khoza
Tumelong Women and Child Health
Program
P O Box 7726
Pretoria 0001 South Africa
Tel: 012 362 2366
Fax: 012 362 0041

Elizabeth Khutleti
Wola Nani
P O Box 255
Diepkloof 1864 South Africa
Tel: 011 938 8370

Peter Lamb
Witbank Hospital
Private Bag X7206
Witbank 1035 South Africa
Tel: 0135 656 2111 x 293
Fax: 0135 656 1316
Cel: 082 936 4794

Dolly Mabusela
Medical University of Southern Africa
Department of Medical Microbiology
P O Box 211
Medunsa 0204 South Africa
Tel: 012 521 3567
Fax: 012 521 5727

Carvie Madikane
Northern Cape Province, Department of Health
Room 212, 2nd Floor, Public Bldg.
Corner Knight & Stead Roads
Kimberley, South Africa
Tel: 0531 80 0666
Fax: 0531 33 814

Mia Malan
SABC Radio
Private Bag X1, SABC Radiopark
Auckland Park 2006 South Africa
Tel: 011 714 3661
Cel: 082 416 9475

Joyce Malope
National Association of People Living with AIDS (NAPWA)–Vaal
c/o 392A Klipspruit
P O Pimville 1808 South Africa
Tel: 011 982 6400
Cel: 082 691 1599
Fax: 016 981 9722

Lydia Masemola
Tembisa AIDS Co-ordination Committee
P O Box 4100
Halfway House 1685 South Africa
Tel: 011 926 6419
Fax: 011 926 2862

Mmampedi Mathibe
Medical University of Southern Africa
Department of Medical Microbiology
P O Box 211
Medunsa 0204 South Africa
Tel: 012 521 3567
Fax: 012 521 5727

Elizabeth McGrory
Population Council
One Dag Hammarskjold Plaza
New York, NY 10017 USA
Tel: 212 339 0604
Fax: 212 755 6052

Jake Moetle
Peri-Natal HIV Research Unit
Baragwanath Hospital
P O Bertsham 2013 South Africa
Tel: 011 933 9165
Fax: 011 938 3984

Brenda Mohale
Wola Nani
P O Box 255
Diepkloof 1864 South Africa
Tel: 011 938 8370

Khatatso Mokoetle
National Progressive Primary Health Care Network (NPPHCN)
P O Box 3209
Braamfontein 2017 South Africa
Tel: 011 403 4647
Cel: 083 601 8229
Fax: 011 403 1832

Mamsi Molefe
National Association of People Living with AIDS (NAPWA)–Vaal
c/o 392A Klipspruit
P O Pimville 1808 South Africa
Tel: 011 982 6400
Cel: 082 691 1599
Fax: 016 981 9722

Jane Moleleki
Northern Cape Province, Department of Health
Room 212, 2nd Floor, Public Bldg.
Corner Knight & Stead Roads
Kimberley, South Africa
Tel: 0531 80 0666
Fax: 0531 33 814

Constance Monedi
Medical University of Southern Africa
Department of Medical Microbiology
P O Box 211
Medunsa 0204 South Africa
Tel: 012 521 3567
Fax: 012 521 5727

Josephine Moremong
Peri-Natal HIV Research Unit
Baragwanath Hospital
P O Bertsham 2013 South Africa
Tel: 011 938 1534
Cel: 083 378 2468

Rebecca Motlatla
National AIDS Directorate
Private Bag X828
Pretoria 0001 South Africa
Tel: 012 312 019
Fax: 012 326 2740

Hector Motsoeneng
Wola Nani
P O Box 255
Diepkloof 1864 South Africa
Tel: 011 938 8370; 011 933 9340

Nokuzola Mqoqi
Reproductive Health Unit
Baragwanath Hospital
P O Bertsham 2013 South Africa
Tel: 011 933 1228
Fax: 011 933 1227

Lungi Msutwana
Western Cape, Department of Health
Mother & Child Healthcare
Private Bag X19
Bellville 7535 South Africa
Tel: 021 948 9050
Fax: 021 949 9611

Adrian Myburgh
Gauteng, Department of Health
AIDS Directorate
Private Bag X085
Marshalltown 2017 South Africa
Tel: 011 355 3384
Fax: 011 355 3385/6

Gloria Nchukana
Eastern Cape, Department of Health
Private Bag X0038
Bisho 5608 South Africa
Tel: 040 609 3458
Fax: 040 635 0072

Nontsha Nciza
Boksburg Councillor
5032 Zathu Street
Vosloorus 1475 South Africa
Tel: 011 863 6766
Cel: 082 783 2023
Fax: 011 899 4052 (c/o Library/Sipho)

Nelly Ntuli
Medical Research Council–Hlabisa
P O Box 198
Mtubatuba 3935 South Africa
Tel: 035 550 0158
Fax: 035 550 1674

Lorna Papo
Northern Province
Department of Health & Welfare
Private Bag X9302
Pietersburg 0700 South Africa
Tel: 015 295 2851
Fax: 015 291 3355

Ilse Pauw
Sex Worker Education and Advocacy Taskforce (SWEAT)
P O Box 373
Woodstock 7915 South Africa
Tel: 021 448 7875
Cel: 083 450 2678
Fax: 021 448 7857

Fatima Rahjman
Centre for Applied Legal Studies (CALS) AIDS Law Project
Private Bag X3
WITS 2050 South Africa
Tel: 011 403 6930
Fax: 011 403 2341

Gita Ramjee
Medical Research Council–Durban
171 Umbilo Road
Durban, South Africa
Tel: 031 241481
Cel: 082 451 0901
Fax: 031 258840

Karen Rotchford
Medical Research Council–Hlabisa
P O Box 198
Mtubatuba 3935 South Africa
Tel: 035 550 0158
Fax: 035 550 1674

Hamilton Sebola
Medical University of Southern Africa
Department of Medical Microbiology
P O Box 211
Medunsa 0204 South Africa
Tel: 012 521 3576
Fax: 012 521 5727

Doreen Senokanyane
Gauteng, Department of Health
Private Bag X085
Marshalltown 2107 South Africa
Tel: 011 355 3333
Fax: 011 355 3338

Thembani Shabangu
Wola Nani
P O Box 255
Diepkloof 1864 South Africa
Tel: 011 938 8370

Nicci Stein
Triangle Project
P O Box 43282
Woodstock 7195 South Africa
Tel: 021 448 3812
Fax: 021 448 4089

Marion Stevens
Women's Health Project
P O Box 1038
Johannesburg 2000 South Africa
Tel: 011 489 9919
Cel: 082 958 2542
Fax: 011 489 9922

Stax Telekoa
National Coalition for Gay & Lesbian Equality
593A Ntombela Street
P O Kwa-Xuma
White City 1868 South Africa

Gaye Tharawan
Population Council
P O Box 138
Pratunam Post Office
Bangkok 10409 Thailand
Tel: 66 2 251 4766
Fax: 66 2 255 5513

Brenda Thompson
National Association of People Living with AIDS (NAPWA)–Vaal
c/o 392A Klipspruit
P O Pimville 1808 South Africa
Tel: 011 982 6400
Cel: 082 691 1599
Fax: 016 981 9722