Mapping the Standards of Care at Microbicide Clinical Trial Sites

Executive Summary

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In addition, various staff of GCM contributed to the project: Sean Philpott provided critical input into the ethics analysis of the report; Anna Forbes authored the box on Cellulose Sulfate; and Mialy Clark provided valuable research assistance.

Finally, we gratefully acknowledge the thousands of women in microbicide trials who confront the realities of HIV in their communities every day. Without their willingness to participate, we could never hope to develop a woman-controlled method of protection against HIV.

The full text of this report is available at http://www.global-campaign.org/clientfiles/SOC.pdf

On the cover: **A counselor at the MDP Africa Centre's Mtubatuba study clinic, KwaZulu Natal, South Africa.**

Photo: PATH / Katie West Slevin

Acronyms and Abbreviations

AIDS	acquired immunodeficiency syndrome
ANC	antenatal care
ART	antiretroviral therapy
ARV	antiretroviral
BV	bacterial vaginosis
CBO	community-based organization
CD4	cluster of differentiation 4
CIOMS	Council for International Organizations of Medical Sciences
CONRAD	Contraceptive Research and Development
CS	Cellulose Sulfate
FHI	Family Health International
GCM	Global Campaign for Microbicides
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trials Network
HSV	herpes simplex virus
IRB	institutional review board
MDP	Microbicides Development Programme
MIRA	Methods for Improving Reproductive Health in Africa
MRC	South African Medical Research Council
MWAMKO	Mwanamke Amua Kuhusu Maisha Yako
NGO	nongovernmental organization
OI	opportunistic infection
Pap/ Pap smear	Papanicolaou test
PEPFAR	US President's Emergency Plan for AIDS Relief
PHC	primary health center
PMTCT	prevention of mother-to-child transmission of HIV
SOC	standards of care
SOP	standard operating procedure
STI	sexually transmitted infection
TB	tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	US Agency for International Development
USD	United States dollar
VIA	visual inspection of the cervix with acetic acid wash
WHO	World Health Organization

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1.0 Background

PATH/Katie West Slevin

Margaret, a study participant and community advisory committee member for the MDP trial site in Mwanza, Tanzania.

In mid-2006, the Global Campaign for Microbicides (GCM) embarked on a project to map the care and prevention services provided to women enrolled in large-scale

(Phase 2b and 3) microbicide effectiveness trials. Our goal was four-fold:

1. To conduct an independent assessment of the health care and prevention services provided to women in the trials—and to some extent, their partners, family, and surrounding community.
2. To better understand the factors that inform care-related decisions at trial sites.
3. To explore the microbicide field's progress toward achieving the ethical aspirations laid out in key ethics guidance documents.
4. To make recommendations to strengthen the field's ability to respond to care-related challenges in the future.

In contrast to many ethics deliberations, our assessment is based not only on principles but on evidence taken directly from the field, where microbicide researchers grapple daily with the often-profound needs of trial participants and their communities.[a] It is our firm belief that we must widen the field of actors and the sources of evidence that provide input into decisions around standards of care. Principles are essential, but ethics deliberation must be grounded in the lived reality of individuals as well. While international debate is helpful, we also need more input from those most closely touched by these trials—those who participate and the communities from which they come. This study is our contribution to collecting concrete field examples to help ground the discussions on standards of care as we move forward in the field of HIV prevention research.

A full report of this effort is available from the Global Campaign for Microbicides at http://www.global-campaign.org/clientfiles/SOC.pdf

a We also benefited greatly from field examples provided through the Partnering for Care in the HIV Prevention Trials Network project, undertaken by Kate MacQueen, Kerry McLoughlin, Patty Alleman, Holly McClain Burke, and Natasha Mack of the Behavioral Sciences Division at Family Health International (http://www.hptn.org/ResearchEthics/PartneringForCare.htm).

2.0 Methods

GCM's approach to the mapping exercise proceeded in three phases. First, we reviewed key documents from seven large-scale effectiveness trials underway in

the developing world, including six microbicide trials and one trial evaluating the diaphragm for HIV prevention. The desk review, which took place from early to mid-2006, included study protocols, procedures manuals, standard operating procedures (SOPs), policy documents, and training manuals for staff. We made every effort to review site-specific, as well as study-wide, SOPs and guidance documents. During this same time period, we interviewed key international staff and study sponsors by telephone, including at least one principal investigator from six of the seven studies. Finally,

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A study nurse at MDP's Africa Centre site—KwaMsane Clinic, KwaZulu Natal, South Africa.

in October and November 2006, we visited six trial sites in four African countries. During site visits, we reviewed additional site-level study documents, interviewed local study investigators and staff, and visited study clinical facilities and local care and support facilities that served the trial communities and to which study participants were referred for additional care.

In selecting sites to visit (see Table 1), we attempted to include a range of realities and study populations—from newly established sites to longstanding research collaborations; from urbanized settings to rural outposts; from sites enrolling women with multiple partners (primarily sex workers) to those recruiting women from family planning and primary health centers (PHCs). We sought a range of country settings across east, west, and southern Africa, where the majority of microbicide effectiveness trials take place. The only microbicide effectiveness trial being implemented in India closed prematurely, before we were able to conduct our planned site visit in early 2007. Similarly, we had originally planned to visit two Family Health International (FHI)-sponsored trial sites in Nigeria, one that was conducting a study of SAVVY®, and a second that was testing the candidate microbicide Cellulose Sulfate (CS). However, the FHI SAVVY® Nigeria study closed in August 2006, before we were able to complete site visits. Further to this, FHI had made the decision to suspend enrollment in Nigeria for its CS study due to low incidence rates and security concerns and was seeking to locate trial sites outside Nigeria in order to continue the study. In light of this, we ultimately decided not to make site visits in Nigeria. We were, however, able to review documents from both studies and interview the country-level investigator of the CS study's Lagos site, who also served on the standards of care advisory group.

All of the participating sites did so voluntarily, and we are grateful to the many staff and investigators who so generously lent their time and support to this effort. At the end of the process, we invited representatives from the participating research staffs, ethicists, and advocates from the GCM Steering Committee to serve as a standards of care advisory group and attend a two-day consultation in South Africa, June 11–12, 2007, to help us interpret our findings and to seek common ground on recommendations for future trials. The recommendations in this report, **HIGHLIGHTED IN**

TABLE 1: Studies and Sites included in Standard-of-Care Mapping Exercise

Study implementer	Study	Study product	Trial sites	Start date (date of first enrollment)	Status (as of October 2008)
CONRAD	CONRAD C03-090	Cellulose Sulfate gel (6%) (also known as Ushercell)	**Cotonou, Benin** Durban, South Africa Kampala, Uganda Bangalore/Bagalkot, India Chennai, India	July 2005	Prematurely stopped by DSMB due to potential of increased risk, January 2007.
FHI	FHI 9784	SAVVY® gel (1% C31G)	Kumasi, Ghana Accra, Ghana Lagos, Nigeria Ibadan, Nigeria	September 2004	Ghanaian sites stopped prematurely in November 2005 by DSMB due to insufficient HIV incidence; Nigerian sites stopped in August 2006 due to futility.
FHI	FHI 9757	Cellulose Sulfate gel (6%) (also known as Ushercell)	Lagos, Nigeria Port Harcourt, Nigeria	November 2004	Prematurely stopped, January 2007, by DSMB; no evidence of potential increased risk.
MDP	MDP 301	PRO 2000 gel (0.5% and 2%)*	**Africa Centre (Umkhanyakude District of KwaZulu Natal), South Africa** **Mwanza, Tanzania (MWAMKO)** Masaka, Uganda Durban, South Africa Johannesburg, South Africa Mazabuka, Zambia	October 2005	DSMB prematurely discontinued 2% arm of the study. Study of 0.5% arm in progress, enrolling and conducting participant follow-up visits. Expected to finish August 2009; results expected late 2009.
Population Council	PC-515	Carraguard® gel	**Gugulethu, South Africa** **Soshanguve, South Africa** Durban, South Africa	March 2005	Study completed March 2007; final results released February 2008; results showed product to be safe but no protective effect against HIV.
HPTN	HPTN 035	PRO 2000 gel (0.5%) and BufferGel	Blantyre, Malawi **Harare, Zimbabwe** Durban, South Africa Hlabisa, South Africa Lilongwe, Malawi Lusaka, Zambia Philadelphia, USA	February 2005	Study finished July 2008; results expected early 2009.
UCSF/WGHI	MIRA	Ortho All-Flex® Arcing Spring latex diaphragm and Replens® lubricant gel	Durban, South Africa Johannesburg, South Africa **Harare, Zimbabwe**	September 2003	Study completed; results released July 2007; diaphragm showed no protective effect against HIV over condoms and risk reduction package provided.

CONRAD, Contraceptive Research and Development; DSMB, Data Safety Monitoring Board; MWAMKO, Mwanamke Amua Kuhusu Maisha Yako (local name for the study); UCSF/WGHI, Women's Global Health Imperative at the University of California, San Francisco. Trial sites in **bold** indicate sites visited as part of the standards of care mapping exercise.

* In 2008, the 2% arm of the MDP trial was suspended due to early indications of no effect of the study product at a 2% concentration.

BLUE BOLDFACE, are "consensus recommendations" that emerged from the consultation.[b] The recommendations **HIGHLIGHTED IN GRAY BOLDFACE** are "authors' recommendations." Authors' recommendations represent ideas that emerged after the consultation, as GCM continued its thinking and refined its conclusions. They do not necessarily represent conclusions that were or would have been rejected by the group. Appendix I, at the end of the text, summarizes all of the recommendations together. A list of the individuals who participated in the consultation is also included as Appendix II.

It is important to place the data gathered here within the context of trial timelines. Of the trial sites included in this exercise, the earliest to begin enrolling was the Harare Methods for Improving Reproductive Health in Africa (MIRA) diaphragm trial in September 2003, and the last was the Mwanza, Tanzania, site of the Microbicides Development

b The consensus recommendations included in this report reflect the collective views of the standards of care advisory group, those who participated in the two-day consultation. They do not necessarily reflect the views of the institutions those individuals represent.

Programme's (MDP) vaginal PRO 2000 gel trial. During this two-and-a-half-year time frame, the ethics discussion on standards of care broadened, and enormous changes took place in the treatment arena. The World Health Organization (WHO) launched its "3 by 5" initiative in 2003, advocating antiretroviral therapy (ART) for 3 million people with AIDS; and in 2004, the US Government made unprecedented sums available for treatment via the President's Emergency Plan for AIDS Relief (PEPFAR). Trials implemented later in this period were then able to take advantage of new partnerships not available prior to 2003.

We also saw that even trials that began early on made changes as they progressed, entering into new partnerships, improving standards of care, and systematically studying challenges to providing care.

In the discussion that follows, we have summarized the findings and recommendations as they relate to specific domains of care and prevention. Afterwards is a brief overview of crosscutting issues that emerged throughout the mapping exercise (all of which are explored in greater detail in the full report), followed by a concluding statement.

3.0 Results from the Standards of Care Mapping Exercise

Overall, we found that the majority of trials had made significant progress toward meeting evolving ethical standards of care and prevention. Ten years ago, the reigning standard of care was provision of counseling and condoms and referral to fragile or non-existent services for care. Today's standards of care may include provision at the study site of a variety of health services, from Pap smears and contraception to treatment of HIV opportunistic infections and ART to provision of non-study related (or ancillary) primary care (e.g., for respiratory and diarrheal infections and childhood immunizations). However, what studies provided and how they did so varied significantly according to a range of factors, including:

- The level of funding available.
- When the trial began and ended.
- National guidelines.
- Sponsor/donor restrictions on funding.
- Provider and researcher attitudes and belief systems.
- Whether a site was co-located with an existing health care facility or was a stand-alone research site.
- The nature of partnerships with other institutions or government to provide care.
- Input from local and international ethics review boards.
- Local realities.
- The level of existing care available in the surrounding community.

Overall, the standards of care mapping exercise documented a range of differences in the care offered to participants across networks and between sites. These variations resulted from differences in the local contexts where trials took place; the diversity of challenges that emerged as a result; and the attitudes and agendas of research institutions, investigators, sponsors, and donors. Specifically, major variations existed between:

- The range of services provided.
- To whom they were provided.
- The types and strength of partnerships forged to provide care during and after trials.
- Where care was provided (study clinic versus referral facility).
- The level of assistance and follow-up provided once someone was referred offsite.
- Whether the trial set aside funding to ensure post-trial access to ART for women who seroconverted during the study.

The Basis of Ethical Research

Three fundamental ethical principles guide research on human beings:

- **Respect for persons,** which acknowledges each individual's right to autonomy and from which follows the requirement for individual informed consent.
- **Beneficence,** which requires that the participants in research are protected from harm and that the benefits of participation to the individual and society are maximized.
- **Justice,** which is generally interpreted to mean that the benefits and burdens of research are fairly distributed among those who participate in trials and those who stand to benefit from results.

3.1 HIV Prevention Services

The ethical principle of beneficence obligates researchers and sponsors to maximize benefits and minimize risks to clinical trial participants.[1] In the context of HIV prevention

trials, this principle extends to the obligation of researchers to help participants minimize their risks of HIV infection during a trial.[c,d] Joint United Nations Programme on HIV/AIDS (UNAIDS) and other ethics guidance documents interpret this mandate as requiring that all participants in HIV prevention trials receive appropriate risk-reduction counseling and access to proven HIV prevention interventions.[e]

Findings

Overall, microbicides studies met or exceeded the ethical obligation to provide access to proven prevention interventions, including risk-reduction counseling, provision of male condoms, and access to female condoms, when requested.

Women enrolled in the trials that were reviewed as part of this exercise received intensive HIV and STI counseling and, in most instances, unlimited free male condoms at one to three month intervals (depending on the study protocol). The repeated interaction with study counselors likely facilitated behavior change because it helped to establish trust, reinforced key messages, and provided opportunities to refine and adapt counseling messages in accordance with ongoing developments in a woman's life. In general, the studies provided high-quality risk-reduction counseling: Staff were well trained and monitored; mechanisms were in place to respect participant confidentiality; and the ratio of counselors to expected client sessions was reasonable.

At most study sites that we visited, female condoms were available when women requested them; however, they were not integrated into risk-reduction counseling, nor were they actively promoted by staff. The exceptions were, first, study sites where female condoms were not yet available in-country (e.g., parts of Nigeria); and second, at the MIRA trial site, where the study protocol discouraged the use of the diaphragm and female condom at the same time. Counselors at the MDP Mwanza site performed female condom demonstrations with the use of a penile model, and since the time of our visit, the MDP site in Unkhanyakude District, South Africa, has made female condoms available in the study clinics and provided all counselors with vaginal models with which to demonstrate insertion and use.

Despite concerns voiced by advocates in the past (including GCM), we found *no* evidence to suggest that study staff ever compromised risk-reduction services in order to "facilitate" the research. In response to concerns over potential conflicts of interest between an investigator's ethical obligation to help women remain uninfected during a trial and the study's scientific "need" for infections to occur in order to evaluate the product's effectiveness, some stakeholders in the HIV prevention research field have recommended that entities outside the research enterprise conduct risk reduction counseling. We however found no evidence to support this potential concern. To the contrary, study counselors appeared more likely to promote condoms so zealously that they sometimes conveyed the impression that it would be inappropriate or unsafe to use the gel alone if condom use were not possible. Also,

PATH/Katie West Slevin

A counseling room at the Empilisweni ("Place of Health") Center for Wellness Studies, the Population Council's study clinic in Gugulethu, South Africa.

c Both the Declaration of Helsinki (Paragraph B 18) and CIOMS (Guideline 8, 2002) highlight the importance of informing participants of the risks and benefits of research and to minimize risk to study participants.

d The South African Medical Research Council (MRC) in its Guidelines on Ethics for Medical Research (Guideline 9.5.2) is specific in its statement that "every effort must be made to provide participants with optimal risk reduction counseling and interventions to prevent HIV infection."

e The new UNAIDS/WHO guidance document on Ethical considerations in biomedical HIV prevention trials requires in Guidance Point 13 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."

it was clear from our site visits that the nurses and counselors working at the sites viewed their first responsibility as the safety and health of their fellow community members—the women participating in the trial.

Beyond what was provided to women who were actively enrolled in the trials, those who were screened out of the trials—that is, women who presented for at least one screening visit, even if they were found ineligible for trial participation or chose not to participate in the trial—also received the tangible benefits of HIV prevention services. At a minimum, these women were offered HIV testing with individualized pre- and post-test counseling, the opportunity to return for at least one additional counseling session and free condoms.

Overall, the studies appeared to have met and exceeded their ethical obligations to provide access to proven prevention interventions. That said, more could still be done to promote and integrate female condoms into the standard prevention package. This would further satisfy the ethical obligation to provide access to proven interventions and would help to generate awareness about an important user-controlled prevention option.

➔ **CONSENSUS RECOMMENDATION:** The female condom should be integrated into the standard prevention package in future and ongoing trials, and provided by sponsors at research sites even where they are not available in the public sector. Greater efforts should be made by studies to introduce female condoms and provide counseling and demonstrations to support use.

BOX 1

Hierarchical Messaging

In hierarchical messaging, counselors tell women to use both gel and a condom at every act of sex; if they absolutely cannot use gel and a condom, they are counseled to use a condom; and if they cannot use a condom, they are encouraged to at least use the gel.

3.2 Other Counseling and Support Issues

Within the context of exploring the prevention package provided to study participants, we discovered a number of additional counseling issues that, while not directly related to standards of care, deserve increased attention from the field. These include messages around gel adherence as it relates to condom use, the collection of sexual behavior and adherence information, counseling on psychosocial issues, and increased support for study staff.

Findings: Messages Given about Gel and Condom Use

Across trial sites, counselors consistently emphasized the unknown effectiveness of the study product to prevent the transmission of HIV/STIs, and reinforced the message that condoms are currently the only known way to prevent sexual transmission of HIV/STIs. Most studies combined counseling on gel use with counseling on condom use by employing a hierarchical message (see Box 1) while others provided separate counseling on gel adherence, and emphasized more strongly the role that consistent gel use plays in the successful completion of the study.

During our site visits, however, we found that messages about gel use were highly inconsistent, especially as they related to condom use, both among staff at the same site and/or between staff and study documents. We also found substantial confusion over what message counselors were to give if women were unable to use condoms. Some investigators expressed the belief that encouraging gel use without condoms, even in instances where condom use is not possible, would be unethical.[f] Not infrequently during our site visits, counselors conveyed the impression that it would be inappropriate or unsafe to use the gel alone if condom use were not possible. Our interviews also suggest that outside bodies such as institutional review boards (IRBs) and donors can influence messages given to participants on gel and condom use. Although not strictly a "standards of care" issue, low adherence to gel

f Contrary to this assertion, it is ethical for investigators to encourage gel use even if women cannot use condoms. By counseling on condom use and risk reduction, investigators meet their key ethical obligations of respect for persons and reciprocal justice. Yet, another of the hallmarks of an ethically designed study is scientific validity. If women never used gel in the absence of condoms, it would not be possible to evaluate the gel's effectiveness—the study's primary question. To be ethical, studies must be able to adequately answer the scientific questions posed. Otherwise, women are needlessly exposed to study-related risks.

use can severely undermine the power of a study to determine a product's effect and highlights the need to develop clear, consistent messages on product adherence and to train staff on how to deliver these messages.

Findings: Collecting Data on Sexual Behavior and Gel and Condom Use

In addition to messages given about gel and condom use, study sites have used a range of approaches to collect data on sexual behavior, gel adherence, and condom use, and both researchers and advocates alike have raised concerns over the impact of these methods on data reliability.

The primary concern is that participants will adapt their answers to what they think the interviewers want to hear, particularly if the same interviewer also provides counseling on gel use, the importance of condom use, and other risk reduction messages. In response to concerns over this concept, frequently termed "social desirability" bias, some studies separated risk reduction counseling from collection of information on sexual behavior and gel use. In some cases, different staff members were assigned these tasks—typically with interviewers or social scientists conducting interviews on sexual behavior and gel use (with or without the use of an audio computer-assisted self-interview, ACASI) and counselors conducting risk reduction counseling. In others, the same staff performed data collection and risk reduction counseling, but the tasks were separated from one another, with the behavioral interviews (where women answered questions about their sexual behavior and adherence to study products) conducted first, followed by the risk reduction counseling.

Findings: Counseling on Psychosocial Issues

Both participants and study staff widely cited access to ongoing relationships with study counselors as one of the major benefits of study participation. Because counseling services in general are very limited in these settings, it is rare that women have previously had the opportunity to build such supportive relationships in which they could discuss personal issues around sexual health and their relationships with partners and family.

The extent to which microbicide trials addressed psychosocial issues, however, varied. Aside from the standard risk reduction and HIV pre- and post-test counseling themes, a number of issues can arise in counseling sessions, including domestic violence, problems with family or partners, suicide, stigma, and issues around HIV disclosure. Some sites addressed these issues by providing support directly or through referral to specialized agencies. Others largely avoided the issues, at least officially. Part of the variation in how sites responded to the psychosocial needs of participants derived from the availability of community resources for psychosocial support.

> "Looking at the patriarchal system we are living in – I don't have power. The most aching part is that I know, I am in research and I know what is good and what is not, but because I'm in that kind of patriarchal marriage I can't have the go ahead to say, 'why can't we use [a] condom?' I cannot it would mean divorce."
>
> — COMMUNITY OUTREACH OFFICER, ZIMBABWE

In addition to the need for psychosocial support for study participants, the need for additional psychosocial support for study counselors and other trial staff is substantial. Staff working in settings with high HIV prevalence typically identify and counsel a very large number of HIV-positive women as part of the screening process. At some sites, two or three out of every four women screened were HIV-positive. Day after day, counselors must confront the emotional burden of helping women come to terms with their diagnosis.

Clinical and counseling staff themselves are often at risk of HIV infection, or may be HIV-positive, and face many of the same challenges as the participants they counsel. This and their personal ongoing relationships with participants result in high job stress and burnout. Some sites provided opportunities for study staff to meet with a staff psychologist; however, greater psychosocial support is needed overall, including counseling and opportunities for staff to debrief.

Ethics guidance from research on gender-based violence tells us that "although preventing harm to [participants] is of primary importance, researchers also have an ethical obligation to minimize possible risks to field staff and

researchers…[and that] the most common risk for fieldworkers…is the emotional toll of listening to women's repeated stories of despair, physical pain, and degradation."[2] It is therefore important to "provide interviewers and research staff with regular opportunities for debriefing, or when necessary, individual counseling…[and] opportunities during training for interviewers to address their own experiences."[3] "Given the high prevalence of gender-based violence globally, it is likely that a substantial proportion of interviewers will have experienced gender-based violence themselves at some point."[4] The same can surely be said for study staff living and working in communities with such high HIV prevalence.

Although staff support is not a classic standards of care issue, it is a clear need identified in this exercise. Many of the staff are affected by or are themselves living with HIV, or may become HIV-positive in the course of the trial. Trial staff need ready access to confidential HIV testing, counseling, and care, and networks conducting trials need clear employee policies for HIV/AIDS care and treatment, including psychosocial and disclosure counseling.

➔ **CONSENSUS RECOMMENDATION:** All staff at future microbicide trials should receive training such as "values clarification" to better prepare them to deal with the sensitive sexual and reproductive issues and domestic violence confronted by participants. This would be likely to improve adherence to product by providing more objective counseling, reducing stigma, and in general, strengthening the quality of counseling.

➔ **CONSENSUS RECOMMENDATION:** Trial sponsors, donors, and research networks should develop and implement standards of care policies for their staff, including guaranteed access to psychosocial support, disclosure counseling, and high-quality HIV care and AIDS treatment. Policies should take measures to ensure confidentiality of trial staffs' HIV status in the same manner they protect trial participants.

★ **GCM RECOMMENDATION:** The field should seek to clarify messaging around gel use, as microbicide trials are premised on the notion that women can and will use microbicides when condom use is not possible.

BOX 2

What is the "Universal Best Standard of Care"?

"Universal best standard of care" is an inherently flawed concept. Definitions of "best" vary greatly, even among developed countries with generally high-quality health care standards. For example, the "best standard of care" one would receive in the US may differ from that in the UK. Comparisons to a universal "best" are therefore misleading. Yet it is fair to say that certain aspects of the care being provided in microbicide trials (e.g., STI management) would generally meet or exceed the "best" standard of care reasonably accessible anywhere in the world by virtually any reasonable definition.

3.3 STI Screening and Care

STIs are proven cofactors that facilitate HIV transmission.[g] Rates of sexual transmission of HIV tend to be highest among populations with poor STI control, as is common among communities hosting microbicide trials. Infections, such as gonorrhea, chlamydia, and syphilis, are usually asymptomatic in women, and thus frequently go untreated, compromising a woman's health and increasing her vulnerability to HIV. Although screening and treatment for syphilis as part of antenatal care is inexpensive and addresses a major cause of morbidity and mortality in infants and mothers, it is largely unavailable to women in sub-Saharan Africa.

According to WHO, prevention and control of STIs should be an integral part of comprehensive sexual and reproductive health services.[5] Likewise, ethics guidance obliges researchers to ensure access to health care services needed for the safe conduct of trials.[6] Because many microbicide trials collect information on STIs as secondary effectiveness endpoints, STI screening and treatment is necessary both as a component of a trial's HIV

g For further discussion on this complex subject, please refer to STI Interventions for Preventing HIV: Appraisal of the Evidence, © World Health Organization (WHO) and Joint United Nations Programme on HIV/AIDS (UNAIDS) 2008, Geneva.

prevention package and as part of its obligation to provide trial-related health services. Providing STI services also offers trials an opportunity to improve the sexual health of women, many of whom suffer from curable STIs that have never been identified or treated.

Findings

STI prevalence is typically high in the communities in which trials take place. Overburdened public services and other barriers, including lack of sufficient staff with STI training and access to effective medications, typically limit women's access to health care. In all but one of these studies, women who came to be screened for participation, (whether or not they were eventually enrolled in a study) at a minimum received highly sensitive diagnostic tests for gonorrhea, chlamydia, and syphilis. The fact that most studies provided STI testing despite the cost (estimated at the time of printing to be 20 USD per woman) demonstrates that one-time STI diagnosis and treatment for all women is feasible, even for those who do not eventually enroll in the study. Women with positive STI results were offered treatment for themselves as well as treatment or referral for their sexual partners. Study staff actively traced and treated the women who tested positive for an STI but did not return to the clinic to receive their test results.

In addition to the initial STI testing provided at screening, women who enrolled in the trials received testing for STIs at regular monthly to quarterly intervals. Symptomatic infections (with laboratory diagnosis) were managed between testing intervals. Testing was also provided for non-sexually transmitted vaginal infections, such as candida (yeast) infections and bacterial vaginosis (BV). Clinicians treated women with effective drugs (usually single dose where indicated). Depending on the site, they offered participants' sexual partners free diagnosis and treatment, referral, or a take-home course of treatment.

Five of nine sites reviewed also provided a course of acyclovir to treat women with symptomatic HSV-2 infection (genital herpes). Overall, the level of STI screening and care that trial participants received in the research setting far exceeded that available in the communities where trials were taking place and was on par with the best STI care available globally.

Some components of this care were a function of the special requirements of research (to evaluate study endpoints) and are neither feasible nor appropriate in a community clinic setting. Other components (such as antenatal syphilis screening and treatment, simple microscopy, single-dose antibiotic treatment for chlamydia, and better management of drug supplies) are sustainable in most settings and providing these services is a viable means to ratchet up standards of STI care for women, thus having a positive impact on wider community health.

"Most [women] come with their partners. They can go to clinic or here [but] they prefer to come here because they don't have to wait. And we're so glad when they come with their partners because it's an opportunity to counsel the partner. [It is] mostly the younger women. Sometimes they will call [their partners] from [the clinic] and say, 'the nurse wants to see you too, come to the clinic'."

— STUDY NURSE, SOUTH AFRICA

➔ **CONSENSUS RECOMMENDATION:** Laboratory screening and treatment for STIs, including gonorrhea, syphilis, and chlamydia at a minimum, should be provided to all women at least once, even those who screen out at enrollment, as a service to the community.

★ **GCM RECOMMENDATION:** Every effort should be made by researchers to build capacity and infrastructure to strengthen STI control in the community. This includes promoting the use of STI guidelines, antenatal screening and treatment for syphilis, advocating for single-dose treatment of STIs where possible, supporting provider training in STI management, and local capacity-building to add speculum exam and simple microscopy to syndromic management.

★ **GCM RECOMMENDATION:** To build program capacity and contribute to improved STI care, researchers should advocate for improved STI services that are appropriate and sustainable; for example, using their influence and trial-related resources for capacity-building and advocacy for accessible, non-stigmatizing services,

including improved STI drug supply management.

3.4 Cervical Screening and Care

All microbicide protocols include visual examination of the vagina and cervix. Complaints of vulvar or vaginal symptoms could signal an adverse reaction to the active agent being studied, so clinicians investigate potential problems visually or with a colposcope, a magnifying scope with a light on it. In conducting this safety and investigatory process among study participants, clinicians also sometimes identify precancerous abnormalities (dysplasia), or less commonly, advanced cervical cancer. In many developing countries, cervical cancer is the most common cause of cancer death among women.[7] HIV-positive women have a greater risk of developing cervical precancer and a faster progression to invasive disease. In the developed world, most women undergo routine cervical screening (usually via Pap smears) to identify cervical abnormalities so that these may be treated before cervical cancer develops.

Integrating cervical screening into microbicide trials is itself not difficult and experience has confirmed that a public health approach to screening and treatment can successfully prevent cervical cancer; however, "screening and early diagnosis will lead to reduced morbidity and mortality only if integrated with follow-up and management of all pre-invasive lesions and cervical cancers detected."[8]

Screening is of little value in communities without the laboratory, diagnostic, and treatment capacity to deal with abnormal findings. In the absence of cervical cancer programs to provide these necessary services once studies end, researchers face an ethical quandary of whether it makes sense to provide screening, and if so, how. A related issue is that HIV-positive women with cervical dysplasia may require more intensive follow-up and treatment than HIV-negative women, a further challenge if they are identified at screening and will not be enrolled.

Findings

In South Africa, the national health system provides cervical screening by Pap smear, diagnosis, and treatment. Correspondingly, the trial sites we visited in South Africa provided cervical screening to all women as part of their study screening procedures. Women

PATH/Katie West Slevin

The Empilisweni ("Place of Health") Center for Wellness Studies, the Population Council's study clinic in Gugulethu, South Africa, was located within the Uluntu Community Center—home to other nongovernmental organizations and a human papillomavirus research study.

with abnormal Paps not otherwise eligible for enrollment were referred to government-run clinics. Those who were eligible or already enrolled in the trial received "fast-track" diagnosis, treatment of dysplasia, and follow-up through gynecological hospitals. The study covered the costs. Trials that provided screening by Pap smear did so annually, a research standard that exceeds WHO and most developed country recommendations for frequency of screening.

Where cervical screening and treatment was not available in the public sector and no options existed for continued management (Tanzania and Benin), trials did not offer these services.

In Zimbabwe, the principle investigator of the HPTN 035 study creatively linked study services to a pilot effort to make cervical screening more broadly available in the community. The HPTN 035 study requires two screening visits. Women eligible for the second screening receive a Pap smear, onsite colposcopy as needed, free treatment, and follow-up. Zimbabwe and other countries now train providers in visual inspection of the cervix with acetic acid wash (a technique known as VIA), a lower-cost screening alternative that provides immediate results and the option for same-day treatment. The "single visit approach" using VIA may be the best way to manage screening and treatment of dysplasia in resource-poor settings and has now been adopted as national policy in Tanzania. Even with VIA, however, services are still needed to manage ongoing follow-up and treatment of dysplasia and invasive cancer.

➔ **CONSENSUS RECOMMENDATION:** At a minimum, future trials should provide cervical screening for participants if some publicly supported cervical cancer prevention services exist, including diagnosis and treatment for dysplasia. In countries where no public cervical screening and treatment services exist, investigators should advocate for and support initiation of needed services. Studies can improve access to services by offering training to public-sector providers in screening colposcopy, including appropriate low-tech approaches such as VIA where they are approved.

3.5 Pregnancy

Frequent pregnancy testing in microbicide trials is necessary to minimize fetal exposure to the study product. Despite efforts to enroll women who do not wish to become pregnant, a certain number of women will inevitably fall pregnant during the course of a study, and most but not all researchers have seen unexpectedly high pregnancy rates among participants—as high as 76 per 100-person-years.[9] Pregnancy rates were highest among women with multiple partners in areas with low contraceptive use. High rates are due in part to the frequent pregnancy testing implemented, which results in the detection of a high number of pregnancies that would otherwise go unnoticed. Approximately one-third of all pregnancies result in early miscarriage without a woman or her provider ever knowing that conception occurred.[10,11]

Pregnancy in microbicide trials raises two issues. First, women who become pregnant are taken off the study product either entirely or for the duration of their pregnancies. If many women become pregnant, the ability of the trial to answer the fundamental question—does the product prevent HIV acquisition?—is significantly reduced. Second, it raises researchers' ethical obligation to address the pregnancies that do occur--for example, counseling on legal and available pregnancy options and access to pregnancy related services.

Most international ethics documents do not address management of pregnancy or counseling on pregnancy options, but some do assert that legal options to terminate pregnancy are relevant to include in a comprehensive care package[12] and that pregnancy should not fundamentally exclude women from participation in research trials.[13]

Findings

Most sites offered referrals for antenatal care (ANC), prevention of mother-to-child transmission of HIV (PMTCT) services, and limited pregnancy counseling in response to observed pregnancy rates. The accessibility and cost of ANC and the legality and availability of termination of pregnancy however varied among the settings we visited.

Generally, participants who became pregnant were allowed to continue with study visits but were taken off-product temporarily. There were two exceptions. The Population Council study discontinued pregnant women from the study completely and the MIRA study allowed the participants to continue diaphragm use throughout their pregnancies. Despite repeated messages that women who became pregnant would no longer be able to use the gel or continue in the study, investigators noted that many women nonetheless expressed surprise to learn that pregnancy would affect their continued use of study product. However, according to anecdotal interviews, staff were not aware of evidence at any site of women seeking to terminate pregnancy merely to remain in the study or on product.

At every site we reviewed, we observed that participants received insufficient information regarding pregnancy options, abortion services (where legal), the risks of unsafe abortion, and the local availability of post-abortion care. Some counselors and nurses provided information about legal abortion services if participants broached the subject, but did not otherwise volunteer the information. Beyond this, study staff had not been adequately trained to provide comprehensive pregnancy options counseling. Given that unsafe abortion is common worldwide, educating women about the dangers of unsafe abortion and where to go for post-abortion care is vital to their health and safety.

"[The most difficult is] seeing women who are taking risks or in bad situations and can't find something in them to move from that situation. She has options but she doesn't know which one to take. The [study] will be over and I won't see that participant and I won't know what happened. But I can't do anything for that, she has to find the right time."

— STUDY COUNSELOR, POPULATION COUNCIL, SOUTH AFRICA

➔ **CONSENSUS RECOMMENDATION:** Trials should provide relevant site-level staff with the necessary training to ensure competency in counseling and provision of contraception, provision of information on all legal pregnancy options, and to understand the relationship between contraceptive use, informed choice, and other study procedures.

➔ **CONSENSUS RECOMMENDATION:** Women who become pregnant should be allowed to stay in the study, and thereby continue to be monitored and receive study-related benefits.

★ **GCM RECOMMENDATION:** Site staff should be trained to inform women of all pregnancy options, including termination of pregnancy where abortion is legal, and to counsel on the dangers of unsafe abortion and when and where to seek care in case of post-abortion complications.

3.6 Contraception

GCM has argued that on-site access to contraception is a reasonable and prudent benefit to provide participants in HIV prevention trials. This is a practical low-cost method of ratcheting up standards of care, and it contributes to optimal study outcomes. However, there is disagreement on whether non-barrier contraceptive methods should be *required* for study participation and decisions on appropriate contraceptive requirements may vary depending on the study product. Although women who do not wish to use contraception can obviously choose to not join a study, some argue that such a strategy challenges women's fundamental right to informed choice on which, if any, method they will use.[14]

Findings

Most trials did not provide contraception at their outset, but added it later by protocol amendment in response to the high pregnancy rates that researchers observed. Approaches to contraception included referral without counseling, referral with counseling, and counseling with provision of methods. Those trials that provided contraception on-site usually provided more than one option, consistent with the mix of methods available locally. Sites that anticipated high pregnancy rates early on—and therefore provided family planning—had the lowest pregnancy rates. However, variations in pregnancy rates also reflected the underlying acceptability of contraceptive use among the study population and the community at large. For instance, pregnancy rates were highest in the West African trials where contraceptive uptake is

generally low. Study staff reported that many of the women enrolled (especially women with multiple partners) preferred condoms over hormonal methods for both disease and pregnancy prevention. No sites routinely offered emergency contraceptive pills, although they were available in the community at all the sites we visited.

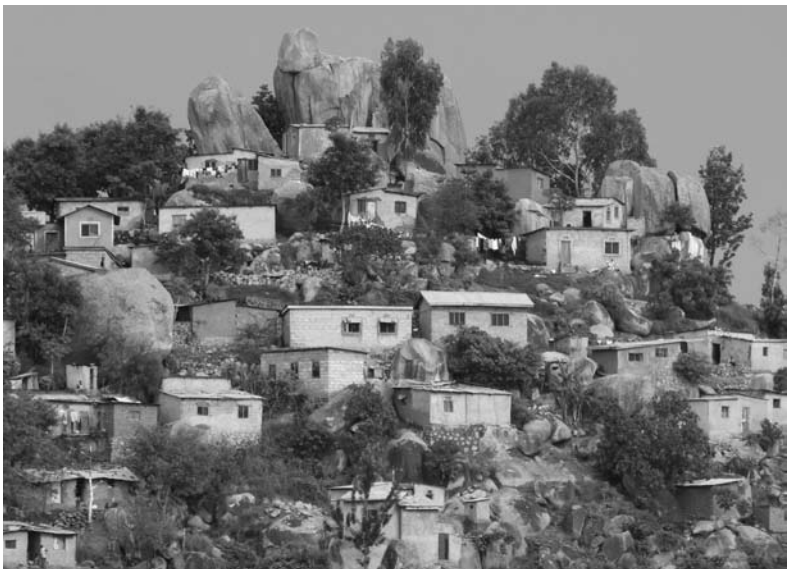
➔ **CONSENSUS RECOMMENDATION:** Microbicide trials have a special obligation to attend to the sexual and reproductive health needs of trial participants, including counseling and provision of safe, appropriate contraception. Avoidance of unwanted pregnancy will also improve trial power and help researchers answer the study questions more effectively.

➔ **CONSENSUS RECOMMENDATION:** Trials should consider providing emergency contraception, including routine integration of counseling on and provision of emergency contraception, as part of contraceptive services. Given to women to keep at home in case of condom failure, lapse in use of regular method, or unplanned, unprotected sex, emergency contraception could lower pregnancy rates, increase study power, and prevent unsafe abortion.

3.7 HIV Care and Treatment

Ten years ago, HIV-positive women who screened out or who became HIV-positive (seroconverted) during trial participation were referred to nongovernmental organizations (NGOs) or community-based organizations (CBOs) for counseling and palliative care. Publicly funded HIV treatment programs did not exist, and ART was not yet available in most parts of Africa. Ten years later, huge increases in resources for HIV/AIDS care have helped governments to establish programs that are largely free and increasingly accessible to those in need, and there is growing ethical consensus that women who seroconvert during microbicide trials should be ensured access to comprehensive HIV care, including ART when appropriate.

Microbicide and diaphragm trials identify two groups of HIV-positive women: those found to be HIV-positive at screening, and those who become infected during the course of their study participation. Regardless of when infection occurs, all women need post-test counseling and psychosocial support to accept their diagnosis and to manage disclosures. They need guidance on risk reduction and positive living. They need information and services for staying healthy; screening for tuberculosis (TB); and information and services for STIs, sexual health, family planning, and managing pregnancy, including PMTCT.



PATH / Katie West Slevin

Typical homes above Lake Victoria in Mwanza, Tanzania.

For women who are found to be HIV-positive at screening, providing clinical staging—and if possible, a CD4 count—is critical to assessing their need for treatment. Some proportion of these women are also likely to need prophylaxis and treatment for opportunistic infections (OIs) and/or ART if medically eligible.

The ethical obligation of researchers to provide care is generally thought to be stronger for women who take part in a study than it is for those who are screened for a study but are found to be ineligible and therefore are never enrolled.[h] However, the care-related needs of women who have recently seroconverted tend to be less than those who have been infected for some time. With more advanced disease, these women may be in need of ART or the other forms of the care described above. Many researchers struggle with this dilemma, and discussions are ongoing about the need to provide increased services for women found ineligible at screening. Many have begun to do so onsite, or have entered into capacity-

h The obligation is greater because the burden participants assume is greater in terms of time and risk. Also, the relationship between the investigator and trial participants is deeper and longer term.

building relationships focused on assisting local care facilities in providing services to the influx of women being identified as HIV-positive by research sites.

Findings

Every trial site that we visited in October and November 2006 had free government HIV/ART services available in the community. These programs tended to be new and overburdened or underutilized, and stigma and long wait times were common barriers to access. While the majority of services were free, in some areas, there were fees associated with accessing care, as in Zimbabwe, where HIV care was free but required costly baseline tests. Social welfare programs exist to cover or help offset these costs, but some complained of difficulties in obtaining the grants. In addition, there were variations in the publicly available services across sites, including where services were offered (in hospitals or PHCs and distance from study sites); waiting times; baseline testing requirements to enroll in programs; and the availability of HIV care such as OI prophylaxis and treatment, antiretrovirals, and other drugs.

Overall, studies offered more HIV services to participants who seroconverted during a trial and were still healthy, but who assumed greater risk and burden by virtue of their trial participation than women found to be HIV-positive at screening. There were some exceptions, however. At one site, clinicians offered CD4 counts to women who were found to be HIV-positive at screening, but not to women who seroconverted during the trial because they were already known to be in a very early stage of the disease.

For women testing HIV-positive at screening, all sites offered extra post-test counseling and referral to HIV/ART programs and other support services, most with at least some monitoring of the uptake of referrals. Some sites also offered study-assisted referrals, where study staff would schedule appointments for or accompany women to referral centers, WHO staging, CD4 counts, OI prophylaxis, and ongoing psychosocial support. One of the reasons cited by study staff for not providing CD4 counts for women who tested HIV-positive at study screening (sites in Tanzania and Zimbabwe) was that government-run ART and HIV care clinics would not accept test results from research studies, but rather, insisted on conducting all baseline tests themselves, resulting in delays for treatment and increased costs.

Many staff with whom we spoke felt the increasing obligation to help women who may already be sick (those who test positive at screening) access care—a sentiment that can be seen in the move toward the provision of more equal care to both groups. One Mwanza site investigator went so far as to say, "Our major obligation is to screened-out women, not to seroconverters."

Despite the availability of additional support, the majority of women who were HIV-positive at screening did not return voluntarily to the study site for additional services. There could be many reasons—for example, they may not have been ready to accept their HIV status; they may have preferred to access care elsewhere; or they may not have felt sick. In at least some studies, if a woman had an abnormal STI or Pap result (Population Council) or a low CD4 count (MDP KwaZulu Natal) and did not return to the clinic, study staff traced them to inform them of their results and encourage them to seek treatment. After study closure, outreach workers at the FHI CS study in Nigeria tracked women who had tested HIV-positive at study screening but had not yet enrolled in a treatment program.

Most of the studies (the exceptions being the Population Council and the FHI SAVVY® study in Nigeria) allowed women who became HIV-positive during the study to remain enrolled and receive trial-related care. All sites offered seroconverters ongoing counseling for positive living and study-assisted referral to ART programs. Some offered OI prophylaxis, CD4 counts, and baseline laboratory studies. However, as stated above, most women did not need these services during the length of the study.

Overall, we found that sites that were co-located or partnered with existing government care facilities were generally able to provide the broadest range of HIV services. Both the women who presented for screening and those enrolled in the CONRAD CS trial in Benin were able to access complete HIV care and ART onsite. This was also true for any HIV-positive men and women in the community (not associated with the trial) who accessed clinic services at this location. This was possible only because the trial clinic was a local STI clinic, which also was one of five HIV care centers

in the city and where this care was already being offered as part of the national AIDS care program. A program supported by the national government and, primarily, the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM).

➔ **CONSENSUS RECOMMENDATION:** Future trials should pursue concrete steps to improve referral systems and facilitate access to government- or NGO-run HIV/ART programs for women who screen HIV-positive at enrollment by providing WHO staging and CD4 counts at the initial screening visit. Trials should consult with government programs and establish formal agreements where possible to avoid the need for repeating HIV and baseline testing and facilitate access to HIV care and treatment programs when required.

➔ **CONSENSUS RECOMMENDATION:** Women who seroconvert should be allowed to stay within the study, and thereby continue to be monitored and receive study-related benefits.

3.8 When Trials End: Continuity Post-Trial

Research ethics guidance has focused almost exclusively on the obligations of investigators to provide care during the lifetime of a study, along with some discussion of the obligation to provide care for women who seroconvert during trial participation. Other than the question of access to effective products and interventions post-trial, most ethics guidance does not discuss participants' continued access to care after the study ends. The reality of women losing care at trial completion, however, poses challenges for both study participants and providers. The degree to which services available *during* the study remain available *after* the study depends on the nature of the service, its cost and appropriateness, its sustainability in local institutions, partnering efforts by researchers, and the extent of the pre-trial planning done in anticipation of the trial's closure.

Findings

Trial sites that are co-located with existing care facilities are better positioned to ensure the continuation of some level of care after the study ends. For example, the Africa Centre, where one of the MDP study sites is located, secured PEPFAR funding for local HIV programs, and the MDP study clinics are adjacent to government health clinics that provide a range of services. As a result, much of the care offered by the study will remain accessible to women after the trial closes. By contrast, where sites have parallel, free-standing research clinics, the possibility of continuity of care poses a greater challenge.

"There was this one woman who I saw at the 24-month celebration. She seroconverted after close-out, 5 months [after she finished participation in the study]. She [isn't enrolled in the study] anymore. She's lucky because we're not closed so I told her she can come to the support group but [we need] a system for what happens to people in the future. To have a [longer] closure period [so that if participants] seroconvert soon after the end of the trial, [they] have somewhere to go."

— STUDY COUNSELOR, SOUTH AFRICA

Even sites that are co-located with existing care facilities, however, can confront challenges caused by the uncertainties of research and funding cycles. The CONRAD Benin site provides an enlightening example of what can happen despite clear efforts to address continuity of care issues up front. CONRAD partnered with an existing project to provide HIV and STI services to high-risk women in Benin. This funding ended in June 2006, and CONRAD took over paying staff-related costs at the clinic as part of a longer-term plan for the Benin Government to assume responsibility for the project at the trial's end. But the sudden closure of the CS trial and termination of its funding threatened both clinics with closure; clinics that still provided important services to high-risk women in the Cotonou community. Fortunately, a new Canadian research project took over staff and services jointly with the national AIDS control program. However, due to a lower degree of funding available to them, the clinics were forced to reduce staff and the services they are able to provide.

Another issue of continuity comes in the form of questions around the sustainability of research centers and research staff. While

concerns about communities being over-researched and the consequences for both scientific integrity and health of the community are valid, so too are concerns over lost opportunities in terms of highly trained staff, well-educated communities, and established research facilities. One major concern is the too-often missed opportunity to expand the capacity of former trial participants, research staff, and community advisors to be advocates and educators in their communities after a trial's end. The HIV prevention research field needs to look toward more creative planning to ensure the transition of resources and sustainability of employment for highly motivated and trained research staffs and communities.

➔ **CONSENSUS RECOMMENDATION:** HIV prevention researchers, sponsors, and donors should make every effort to use microbicide trials as an opportunity to strengthen and improve local standards of care and services in host communities, and in host countries where possible. The minimum objective should be to incrementally improve care in a sustainable fashion to reduce global disparities in health.

➔ **CONSENSUS RECOMMENDATION:** Future trials should seek opportunities to co-locate or partner with existing local care facilities in order facilitate easier access to referral services for participants, strengthen opportunities for care-related synergies, and build long-term standards of care capacity in the host community. Establishing partnerships with government and local care facilities and supporting existing service-providing NGOs or public clinics to build up their services at the beginning of a trial could help address long-term care needs after trial closures.

➔ **CONSENSUS RECOMMENDATION:** Sponsors and donors should develop creative means, such as a human resources database of staff curriculum vitae, to ensure that human resources capacity built up during trials is protected and every effort is made to absorb existing capacity of trained staff into new trials before hiring new staff. Trained and experienced staff improve the quality of care provided at trial sites, and concerted efforts should be made to keep these highly skilled individuals employed for the benefit of the studies and the microbicides field overall.

➔ **CONSENSUS RECOMMENDATION:** Trial sites need to develop concrete plans surrounding trial closure, including plans for transitioning all trial volunteers into public health sector or NGO-provided services, and providing formal acknowledgement at the trial's closure for their participation in the study. Trials should explore ways to mobilize trial participants during and after the study closure as community assets, including providing roles as peer educators, community advisory board members, etc.

3.9 Overarching Issues

In our attempt to map the standards of care and prevention at large-scale microbicides trials, we identified a number of overarching issues that have implications across a range of care-related domains. These include:

- Confusion over the ethical concept of "undue inducement" and how this influences care-related decisions.
- The provision of non study-related care by trial staff in settings where healthcare can be difficult to access.
- The impact of donor policies and restrictions on care-related decisions.
- The need to strengthen avenues for community input into decisions around standard of care.
- The improvement of local health care infrastructure and community-level public health programs through co-locating research sites and/or partnering with existing care facilities.
- The corollary need to strengthen mechanisms of referral so that women can actually access care.
- The need to examine the benefits of including and providing services for male partners.
- Managing research-related harms, including social harms.

The full report of the standards of care mapping exercise explores each of these topics in greater depth (available at http://www.global-campaign.org/clientfiles/SOC.pdf). Each raises important and complex issues that deserve more discussion than can be accommodated in this summary. We reproduce here however, the

consensus and author recommendations that address items relevant to these issues. A full list of recommendations is available in Appendix I.

➔ **CONSENSUS RECOMMENDATION:** All future studies, and ongoing studies where feasible, should explicitly define standards of care that will be provided at each trial site; the broad elements of care can be described in the protocol, while specific elements can be written into site standard operating procedures. Community voices should be sought and integrated into standards of care decision-making at every stage of the trial design and implementation.

➔ **CONSENSUS RECOMMENDATION:** Future trials should develop and implement clear policies about how research-related harms (both acute and long-term) will be handled, and issues of compensation and legal liability should be clarified and revisited when necessary, as unforeseen issues may arise with newer-generation products.

➔ **CONSENSUS RECOMMENDATION:** Trials should continue to undertake more proactive efforts to facilitate women's ability to successfully access care provided through referrals and should strive to monitor the outcomes of referral systems to identify best practices and improve uptake of services. Assisted referral should become the minimum standard, including site-specific measures such as providing initial referral and follow-up letters, transportation to referral providers, or accompaniment of women directly.

★ **GCM RECOMMENDATION:** More creative planning with the community is needed at the beginning of a trial to determine how best to transition the resources of a stand-alone research clinic that will not be used for other studies, such as use of a renovated building by the community (government, local community-based organization, or NGO), donating equipment to public clinics to continue an improved level of care in a sustainable way, and possible transition of trained staff to community care settings with some financial support for a transitional period.

★ **GCM RECOMMENDATION:** Field testing and operational research are needed to determine how to operationalize meaningful participation of community and trial participants in care-related decisions from the beginning, including how to equitably share decision-making. Multiple options such as formative research conducted by and with the community, rapid participatory assessment, and participatory "games" to help rank priorities and understand tradeoffs in care should be considered, tried, and rigorously evaluated.

★ **GCM RECOMMENDATION:** Sponsors and funders should provide funding for and encourage researchers and site staff to develop, implement, and monitor the effects of locally appropriate interventions for male partners of women participating in microbicide and diaphragm trials. The goal should be to improve recruitment, retention, and adherence of women; decrease potential social harms; provide at least minimal services to men to increase their knowledge of HIV/STIs; and improve public health in the host community. That being said, a woman's right to decide whether or not to involve her partner(s) should be respected.

★ **GCM RECOMMENDATION:** Researchers and sponsors should develop clear policies to address non-physical harms (psychological, social, and economic) resulting from microbicide trial participation. Sponsors should be liable for costs associated with trial-related injuries and be required to pay for them or have insurance to cover the costs.

★ **GCM RECOMMENDATION:** Donors should be encouraged to develop and implement funding policies that are clear and understandable, that are objectively and scientifically based, and that enable and encourage researchers to ratchet up the local standards of care in a manner that is sustainable even after a study ends.

★ **GCM RECOMMENDATION:** Donors should make funding available, within reason, that can be used for the provision of non-trial related services, including non-study related and post-trial treatment and care, as these services both increase participant recruitment and retention and improve the standards of care in the local community.

4.0 Conclusion

Looking back over the history of microbicide research, we can ask: Is the field making ethical progress? The answer, according to this exercise, is yes. Overall, women are

receiving high-quality risk reduction and counseling services, provision of male condoms (and in some instances, female condoms), STI and reproductive health care, and family planning. When found to be HIV-positive, women are being assisted with accepting their diagnosis and enrolling in local care and support and antiretroviral (ARV) programs (if needed)—and many sites are actively attempting to expand services available for women who are HIV-positive at screening. In most instances, researchers are making valiant efforts to attend to the care needs of the women enrolled in their trials and are exploring creative and innovative solutions to providing care to participants and improving local care environments in the face of hard realities.

Yet certain areas identified through this mapping exercise call for further improvement. While current practice has improved on lessons learned from earlier trials, local community involvement, from the conception of a trial onward, is still insufficient. Decision-making on standards of care is often obscured at the top, with ill-defined or inconsistent donor policies that restrict what is considered "possible" and the ability to meet ethical demands. The root causes of disintegrating health systems, such as poverty and gender inequalities, in which trials are embedded are not adequately acknowledged or addressed. And as a field, we have not found a satisfactory way to ensure that women who seroconvert during a prevention trial can actually access HIV care and treatment *after* the study is over.

Those in the field of HIV prevention research have an opportunity to learn from each other and the obligation to use that knowledge to improve future trials. There is much they can do: create strong linkages or co-locate with local care facilities, with a focus on capacity-building and sustainability; use referrals as a mechanism for care, while addressing the barriers to accessing that care; provide additional support to study staff; and look at real-life examples of how others in HIV prevention research have succeeded or failed. We urge the field to consider the recommendations herein and to use microbicide trials as an opportunity to strengthen and improve local standards of care in communities hosting research trials.

MDP Africa Centre staff practice a microbicides song they composed for a Red Ribbon public outreach event that was held in Mtubatuba, South Africa.

PATH/Katie West Slevin

APPENDIX I. Consensus and Author Recommendations

The recommendations in this report **HIGHLIGTED IN BLUE BOLDFACE** are "consensus recommendations" that emerged from the Johannesburg consultation. The recommendations **IN GRAY BOLDFACE** are "authors' recommendations," which represent ideas that emerged after the consultation, as GCM continued its thinking and refined its conclusions.

➔ **CONSENSUS RECOMMENDATION**	HIV prevention researchers, sponsors, and donors should make every effort to use microbicide trials as an opportunity to strengthen and improve local standards of care and services in host communities, and in host countries where possible. The minimum objective should be to incrementally improve care in a sustainable fashion to reduce global disparities in health.
➔ **CONSENSUS RECOMMENDATION:**	All future studies, and ongoing studies where feasible, should explicitly define standards of care that will be provided at each trial site; the broad elements of care can be described in the protocol, while specific elements can be written into site standard operating procedures. Community voices should be sought and integrated into standards of care decision-making at every stage of the trial design and implementation.
➔ **CONSENSUS RECOMMENDATION:**	Microbicide trials have a special obligation to attend to the sexual and reproductive health needs of trial participants, including counseling and provision of safe, appropriate contraception. Avoidance of unwanted pregnancy will also improve trial power and help researchers answer the study questions more effectively.
➔ **CONSENSUS RECOMMENDATION:**	Trials should provide relevant site-level staff with the necessary training to ensure competency in counseling and provision of contraception, provision of information on all legal pregnancy options, and to understand the relationship between contraceptive use, informed choice, and other study procedures.
➔ **CONSENSUS RECOMMENDATION:**	Future trials should seek opportunities to co-locate or partner with existing local care facilities in order facilitate easier access to referral services for participants, strengthen opportunities for care-related synergies, and build long-term standards of care capacity in the host community. Establishing partnerships with government and local care facilities and supporting existing service-providing NGOs or public clinics to build up their services at the beginning of a trial could help address long-term care needs after trial closures.
➔ **CONSENSUS RECOMMENDATION:**	The female condom should be integrated into the standard prevention package in future and ongoing trials, and provided by sponsors at research sites even where they are not available in the public sector. Greater efforts should be made by studies to introduce female condoms and provide counseling and demonstrations to support use.
➔ **CONSENSUS RECOMMENDATION:**	Trials should consider providing emergency contraception, including routine integration of counseling on and provision of emergency contraception, as part of contraceptive services. Given to women to keep at home in case of condom failure, lapse in use of regular method, or unplanned, unprotected sex, emergency contraception could lower pregnancy rates, increase study power, and prevent unsafe abortion.
➔ **CONSENSUS RECOMMENDATION:**	Future trials should pursue concrete steps to improve referral systems and facilitate access to government- or NOG-run HIV/ART programs for women who screen HIV-positive at enrollment by providing WHO staging and CD4 counts at the initial screening visit. Trials should consult with government programs and establish formal agreements where possible to avoid the need for repeating HIV and baseline testing and facilitate access to HIV care and treatment programs when required.
➔ **CONSENSUS RECOMMENDATION:**	At a minimum, future trials should provide cervical screening for participants if some publicly supported cervical cancer prevention services exist, including diagnosis and treatment for dysplasia. In countries where no public cervical screening and treatment services exist, investigators should advocate for and support initiation of needed services. Studies can improve access to services by offering training to public-sector providers in screening colposcopy, including appropriate low-tech approaches such as VIA where they are approved.
➔ **CONSENSUS RECOMMENDATION:**	Laboratory screening and treatment for STIs, including gonorrhea, syphilis, and chlamydia at a minimum, should be provided to all women at least once, even those who screen out at enrollment, as a service to the community.
➔ **CONSENSUS RECOMMENDATION:**	All staff at future microbicide trials should receive training such as "values clarification" to better prepare them to deal with the sensitive sexual and reproductive issues and domestic violence confronted by participants. This would be likely to improve adherence to product by providing more objective counseling, reducing stigma, and in general, strengthening the quality of counseling.
➔ **CONSENSUS RECOMMENDATION:**	Sponsors and donors should develop creative means, such as a human resources database of staff curriculum vitae, to ensure that human resources capacity built up during trials is protected and every effort is made to absorb existing capacity of trained staff into new trials before hiring new staff. Trained and experienced staff improve the quality of care provided at trial sites, and concerted efforts should be made to keep these highly skilled individuals employed for the benefit of the studies and the microbicides field overall.
➔ **CONSENSUS RECOMMENDATION:**	Trial sponsors, donors, and research networks should develop and implement standards of care policies for their staff, including guaranteed access to psychosocial support, disclosure counseling, and high-quality HIV care and AIDS treatment. Policies should take measures to ensure confidentiality of trial staffs' HIV status in the same manner they protect trial participants.

➔ **CONSENSUS RECOMMENDATION:**	Future trials should develop and implement clear policies about how research-related harms (both acute and long-term) will be handled, and issues of compensation and legal liability should be clarified and revisited when necessary, as unforeseen issues may arise with newer-generation products.
➔ **CONSENSUS RECOMMENDATION:**	Trials should continue to undertake more proactive efforts to facilitate women's ability to successfully access care provided through referrals and should strive to monitor the outcomes of referral systems to identify best practices and improve uptake of services. Assisted referral should become the minimum standard, including site-specific measures such as providing initial referral and follow-up letters, transportation to referral providers, or accompaniment of women directly.
➔ **CONSENSUS RECOMMENDATION:**	Women who become pregnant should be allowed to stay in the study, and thereby continue to be monitored and receive study-related benefits.
➔ **CONSENSUS RECOMMENDATION:**	Women who seroconvert should be allowed to stay within the study, and thereby continue to be monitored and receive study-related benefits.
➔ **CONSENSUS RECOMMENDATION:**	Trial sites need to develop concrete plans surrounding trial closure, including plans for transitioning all trial volunteers into public health sector or NGO-provided services, and providing formal acknowledgement at the trial's closure for their participation in the study. Trials should explore ways to mobilize trial participants during and after the study closure as community assets, including providing roles as peer educators, community advisory board members, etc.
★ **GCM RECOMMENDATION:**	More creative planning with the community is needed at the beginning of a trial to determine how best to transition the resources of a stand-alone research clinic that will not be used for other studies, such as use of a renovated building by the community (government, local community-based organization, or NGO), donating equipment to public clinics to continue an improved level of care in a sustainable way, and possible transition of trained staff to community care settings with some financial support for a transitional period.
★ **GCM RECOMMENDATION:**	Site staff should be trained to inform women of all pregnancy options, including termination of pregnancy where abortion is legal, and to counsel on the dangers of unsafe abortion and when and where to seek care in case of post-abortion complications
★ **GCM RECOMMENDATION:**	The field should seek to clarify messaging around gel use, as microbicide trials are premised on the notion that women can and will use microbicides when condom use is not possible.
★ **GCM RECOMMENDATION:**	Every effort should be made by researchers to build capacity and infrastructure to strengthen STI control in the community. This includes promoting the use of STI guidelines, antenatal screening and treatment for syphilis, advocating for single-dose treatment of STIs where possible, supporting provider training in STI management, and local capacity-building to add speculum exam and simple microscopy to syndromic management.
★ **GCM RECOMMENDATION:**	To build program capacity and contribute to improved STI care, researchers should advocate for improved STI services that are appropriate and sustainable; for example, using their influence and trial-related resources for capacity-building and advocacy for accessible, non-stigmatizing services, including improved STI drug supply management.
★ **GCM RECOMMENDATION:**	Field testing and operational research are needed to determine how to operationalize meaningful participation of community and trial participants in care-related decisions from the beginning, including how to equitably share decision-making. Multiple options such as formative research conducted by and with the community, rapid participatory assessment, and participatory "games" to help rank priorities and understand tradeoffs in care should be considered, tried, and rigorously evaluated.
★ **GCM RECOMMENDATION:**	Sponsors and funders should provide funding for and encourage researchers and site staff to develop, implement, and monitor the effects of locally appropriate interventions for male partners of women participating in microbicide and diaphragm trials. The goal should be to improve recruitment, retention, and adherence of women; decrease potential social harms; provide at least minimal services to men to increase their knowledge of HIV/STIs; and improve public health in the host community. That being said, a woman's right to decide whether or not to involve her partner(s) should be respected.
★ **GCM RECOMMENDATION:**	Researchers and sponsors should develop clear policies to address non-physical harms (psychological, social, and economic) resulting from microbicide trial participation. Sponsors should be liable for costs associated with trial-related injuries and be required to pay for them or have insurance to cover the costs.
★ **GCM RECOMMENDATION:**	Donors should be encouraged to develop and implement funding policies that are clear and understandable, that are objectively and scientifically based, and that enable and encourage researchers to ratchet up the local standards of care in manner that is sustainable even after a study ends.
★ **GCM RECOMMENDATION:**	Donors should make funding available, within reason, that can be used for the provision of non-trial related services, including non-study related and post-trial treatment and care, as these services both increase participant recruitment and retention and improve the standards of care in the local community.

APPENDIX II. Global Campaign for Microbicides' Standards of Care Workshop: Participant List

(Heia Safari Ranch, Johannesburg, South Africa, June 11-12, 2007)

Participant Name	Affiliation	Country
Khatija Ahmed	University of Limpopo/Setshaba Research Centre	South Africa
Deborah Barron	Global Campaign for Microbicides	South Africa
Manju Chatani	African Microbicides Advocacy Group	Ghana
Anne Coletti	Family Health International	United States
Dázon Dixon Diallo	SisterLove, Inc.	United States
Zaynab Essack	HIV/AIDS Vaccine Ethics Group	South Africa
Michelle Folsom	PATH	South Africa
Barbara Friedland	Population Council	United States
Mitzy Gafos	The Africa Centre for Health and Population Studies/ Microbicides Development Programme	South Africa
Lori Heise	Global Campaign for Microbicides	United States
Pauline Irungu	Global Campaign for Microbicides	Kenya
Naomi Lince	Ibis Reproductive Health	South Africa
Margaret Mlingo	University of Zimbabwe-University of California, San Francisco Collaborative Research Project/ HIV Prevention Trials Network	Zimbabwe
John Mutsambi	Global Campaign for Microbicides	Zimbabwe
Folasade Ogunsola	University of Lagos, College of Medicine	Nigeria
Sean Philpott	Global Campaign for Microbicides	United States
Shira Saperstein	The Moriah Fund	United States
Charles Shagi	London School of Hygiene and Tropical Medicine/National Institute for Medical Research/ African Medical and Research Foundation Collaborative Research Projects/ Microbicides Development Programme	Tanzania
Katharine Shapiro	Global Campaign for Microbicides	India
Jerome Singh	Centre for AIDS Prevention Research in South Africa	South Africa
Cathy Slack	HIV/AIDS Vaccine Ethics Group	South Africa
Morenike Ukpong	Nigeria HIV Vaccine and Microbicides Advocacy Group	Nigeria
Lut Van Damme	Contraceptive Research and Development	United States
Constancia Watadzaushe	University of Zimbabwe-University of California, San Francisco Collaborative Research Project/ Methods for Improving Reproductive Health in Africa	Zimbabwe
Katie West	Global Campaign for Microbicides	United States
Sydney West	Global Campaign for Microbicides	United States

Endnotes

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In a visit to the traditional bar she runs with her sister-in-law, a participant in the MDP MWAMKO study told us that she had never gone for any type of women's health care before joining the study.

PATH / Katie West Slevin

"In [another study] there was a woman participant [who was very sick], she was really on death's door and needed to be admitted to the hospital. But, it was not in the budget and we had no pre-approved way to pay for it. The investigator covered the admission cost, antibiotics, etcetera, and she survived. . . We got our wrists slapped because it wasn't part of the budget and protocol and could be perceived as coercive, 'if you get sick, the study will take care of you'. But what are you supposed to do?"

—INTERNATIONAL INVESTIGATOR

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