Mapping the Standards of Care at Microbicide Clinical Trial Sites
“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
Acknowledgments

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Site principal investigators and their staff were extremely generous with their time during our site visits, providing multiple interviews and access to their staff, facilities, and contacts with community health facilities: Fernand Guédou at the CONRAD site in Cotonou, Benin; Mike Chirenje and Margaret Mlingo at the HPTN Harare, Zimbabwe, site; Agnes Chidanyika at the Methods for Improving Reproductive Health in Africa Harare site; Mitzy Gafos at the MDP site in Umkhanyakude District, South Africa; Andrew Valleley at the MDP site in Mwanza, Tanzania; Lydia Altini and Alana de Cock at the Population Council Gugulethu site in Cape Town, South Africa; and Khadija Ahmed at the Soshanguve, South Africa, Population Council site. Folsade Obunsola at the FHI Cellulose Sulfate site in Lagos, Nigeria, also shared materials with us and participated in a lengthy telephone interview. We are particularly indebted to site staff, including the many clinicians and counselors who spent long hours with us.

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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.
### Acronyms and Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>ANC</td>
<td>antenatal care</td>
</tr>
<tr>
<td>AMREF</td>
<td>African Medical Research Foundation</td>
</tr>
<tr>
<td>ART</td>
<td>antiretroviral therapy</td>
</tr>
<tr>
<td>AZT</td>
<td>zidovudine (formerly azidothymidine)</td>
</tr>
<tr>
<td>BV</td>
<td>bacterial vaginosis</td>
</tr>
<tr>
<td>CBO</td>
<td>community-based organization</td>
</tr>
<tr>
<td>CD4</td>
<td>cluster of differentiation 4</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Council for International Organizations of Medical Sciences</td>
</tr>
<tr>
<td>CONRAD</td>
<td>Contraceptive Research and Development</td>
</tr>
<tr>
<td>CS</td>
<td>Cellulose Sulfate</td>
</tr>
<tr>
<td>CT</td>
<td>chlamydia</td>
</tr>
<tr>
<td>DAIDS</td>
<td>Division of AIDS, US National Institutes of Health</td>
</tr>
<tr>
<td>Depo</td>
<td>Depo-Provera contraceptive injection</td>
</tr>
<tr>
<td>DFID</td>
<td>UK Department for International Development</td>
</tr>
<tr>
<td>DIST</td>
<td>Dispensaire Pour les Maladies Sexuellement Transmissibles (sexually transmitted infection reference clinic for Benin's national AIDS control program)</td>
</tr>
<tr>
<td>DoH</td>
<td>Department of Health</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
</tr>
<tr>
<td>FBC</td>
<td>full blood count</td>
</tr>
<tr>
<td>FHI</td>
<td>Family Health International</td>
</tr>
<tr>
<td>GCM</td>
<td>Global Campaign for Microbicides</td>
</tr>
<tr>
<td>GFATM</td>
<td>Global Fund to Fight AIDS, Tuberculosis and Malaria</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HPTN</td>
<td>HIV Prevention Trials Network</td>
</tr>
<tr>
<td>HPV</td>
<td>human papillomavirus</td>
</tr>
<tr>
<td>HSV</td>
<td>herpes simplex virus</td>
</tr>
<tr>
<td>IRB</td>
<td>institutional review board</td>
</tr>
<tr>
<td>KOH</td>
<td>potassium hydroxide</td>
</tr>
<tr>
<td>LEEP</td>
<td>loop electrosurgical excision procedure</td>
</tr>
<tr>
<td>LFT</td>
<td>liver function test</td>
</tr>
<tr>
<td>MDP</td>
<td>Microbicides Development Programme</td>
</tr>
<tr>
<td>MIRA</td>
<td>Methods for Improving Reproductive Health in Africa</td>
</tr>
<tr>
<td>MOU</td>
<td>memorandum of understanding</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>MTN</td>
<td>Microbicide Trials Network</td>
</tr>
<tr>
<td>MWAMKO</td>
<td>Mwanamke Amua Kuhusu Maisha Yako</td>
</tr>
<tr>
<td>NAAA</td>
<td>nucleic acid-based laboratory testing</td>
</tr>
<tr>
<td>NG</td>
<td>gonorrhea</td>
</tr>
<tr>
<td>NGO</td>
<td>nongovernmental organization</td>
</tr>
<tr>
<td>NICHD</td>
<td>National Institute of Child Health and Human Development</td>
</tr>
<tr>
<td>NIDA</td>
<td>National Institute on Drug Abuse, US National Institutes of Health</td>
</tr>
<tr>
<td>NIH</td>
<td>US National Institutes of Health</td>
</tr>
<tr>
<td>NIMH</td>
<td>National Institute of Mental Health, US National Institutes of Health</td>
</tr>
<tr>
<td>OCP</td>
<td>oral contraceptive pill</td>
</tr>
<tr>
<td>OI</td>
<td>opportunistic infection</td>
</tr>
<tr>
<td>Pap/</td>
<td>Papanicolaou test</td>
</tr>
<tr>
<td>Pap smear</td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>PEPFAR</td>
<td>US President's Emergency Plan for AIDS Relief</td>
</tr>
<tr>
<td>PHC</td>
<td>primary health center</td>
</tr>
<tr>
<td>PID</td>
<td>pelvic inflammatory disease</td>
</tr>
<tr>
<td>PLWHA</td>
<td>people living with HIV/AIDS</td>
</tr>
<tr>
<td>PMTCT</td>
<td>prevention of mother-to-child transmission of HIV</td>
</tr>
<tr>
<td>PNLS</td>
<td>Programme Nationale de Lutte Contre le Sida (Benin's national AIDS control program)</td>
</tr>
<tr>
<td>RPR</td>
<td>rapid plasma regain (a screening test for syphilis)</td>
</tr>
<tr>
<td>SOC</td>
<td>standards of care</td>
</tr>
<tr>
<td>SOP</td>
<td>standard operating procedure</td>
</tr>
<tr>
<td>STI</td>
<td>sexually transmitted infection</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TOP</td>
<td>termination of pregnancy</td>
</tr>
<tr>
<td>TV</td>
<td>trichomonas</td>
</tr>
<tr>
<td>UCSF</td>
<td>University of California, San Francisco</td>
</tr>
<tr>
<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS</td>
</tr>
<tr>
<td>USAID</td>
<td>US Agency for International Development</td>
</tr>
<tr>
<td>USD</td>
<td>United States dollar</td>
</tr>
<tr>
<td>UTI</td>
<td>urinary tract infection</td>
</tr>
<tr>
<td>UZ-UCSF</td>
<td>University of Zimbabwe-University of California, San Francisco</td>
</tr>
<tr>
<td>VCT</td>
<td>voluntary counseling and testing</td>
</tr>
<tr>
<td>VIA</td>
<td>visual inspection of the cervix with acetic acid wash</td>
</tr>
<tr>
<td>WGHI</td>
<td>Women's Global Health Imperative</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WMA</td>
<td>World Medical Association</td>
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Katherine proudly wears her MWAMKO t-shirt. MWAMKO is the local name given to the MDP study site in Mwanza, Tanzania.
1.0 Introduction

In recent years, the relentless march of AIDS and the resurgence of tuberculosis (TB) and malaria have focused increased attention on the neglected diseases of poverty.

This concern has been accompanied by a welcome surge in funding to combat these diseases. Both governments and philanthropic foundations have invested billions of dollars to support novel intervention strategies, like insecticide-treated bed nets, and to fund massive research programs to develop new diagnostics, more effective drugs, and preventive strategies like vaccines. As a result, the past decade has witnessed a ballooning in the number of externally sponsored clinical trials taking place in developing countries.

Clinical experimentation with human beings raises complex ethical issues regardless of where a trial takes place. But the issues are even more complex when the research enrolls vulnerable populations living and working in conditions of extreme poverty. Investigators testing new strategies to prevent HIV or treat drug-resistant TB must go to where such infections flourish—frequently the shantytowns, bars, and rural outposts of countries like Cambodia, Malawi, or Zimbabwe. These countries struggle to provide even the most basic health care for their citizens: the average per capita expenditure on health in Malawi is 58 USD compared to 2,560 USD in the United Kingdom. Many of their health facilities lack skilled personnel, adequate equipment, and necessities like clean water. It comes as no surprise then that the prospect of conducting complex clinical trials in such settings poses thorny issues of distributive justice, basic fairness, and balancing risks and benefit.

A key question raised by such trials is what is the ethical obligation of investigators and trial sponsors to attend to the health and welfare needs of trial participants? Is it sufficient for an investigator to provide only the health care and services necessary to conduct the trial safely and to evaluate the specific disease under study? What happens if a participant presents with a health condition unrelated to the objectives of the trial? Does the wealth of the trial sponsor or the neediness of the participants make a difference to our ethical calculus? What is the obligation of researchers, if any, to individuals who volunteer but prove ineligible to participate in a trial? Upwards of one-third of all people who volunteer to participate in HIV prevention trials in parts of Africa screen out as ineligible because they are already HIV-infected. Do trials have an obligation to them?

Questions like these form the core of recent debates surrounding the ethics of clinical research, especially as it involves trials sponsored by industrial world nations and conducted among people in Africa or Asia. Clearly, citizens in these settings stand to benefit from such trials—researchers design such trials specifically to address the diseases that plague these settings. Often, no large pharmaceutical company stands to profit from this research. Most trials addressing neglected diseases—especially those focused on prevention—are conducted by public health researchers with government or philanthropic funds, not private companies. Nonetheless, such trials raise vexing questions on the extent to which the research can and should help rectify longstanding inequities in access to global health resources. Expecting too much could undermine the ability and willingness of donors and investigators to take on the challenge of researching neglected diseases. Expecting too little raises the prospect of exploitation and ethics violation.

Negotiating this fine line has been a key aspect of the ethics program of the Global Campaign for Microbicides (GCM)—a citizen-led movement that works to expand women’s options for HIV prevention and to encourage civil society engagement in the scientific process. Microbicides are products that could reduce the transmission of HIV and other sexually transmitted diseases when used in the vagina or rectum prior to sex. Presently, there are roughly two dozen candidate microbicides under development, including three that are currently in large-scale clinical trials in Africa and Asia (for more information on microbicide...
A safe, effective microbicide could transform HIV prevention by providing a method of protection that women could use without the active cooperation of their male partners. Such an innovation would be especially critical for married women and for women with regular sexual partners. Research the world over confirms that it is in these emotionally important relationships that condom use is especially difficult to initiate and sustain.

In addition to mobilizing political and financial support for increased microbicide research, GCM works to ensure that the research enterprise fully respects the rights and interests of trial participants, host communities, and future microbicide users. For more than a decade, GCM has been at the forefront of identifying, analyzing, and building consensus around various ethical dilemmas posed by research into new HIV prevention strategies. HIV prevention trials pose a unique set of challenges: they enroll healthy rather than sick people; they deal with a highly feared and stigmatizing disease; and they must take place in settings where the risk of infection is high. Too often, the very factors that conspire to elevate HIV risk—poverty, high prevalence of other sexually transmitted infections (STIs), frequent migration, women’s subordination, low literacy, and drug and alcohol use—make research in these settings especially difficult.

HIV prevention research also takes place against an ever-shifting terrain. In 1994, when GCM helped convene the first international consultation on practical and ethical dilemmas in microbicide trials, the question of whether sponsors have an obligation to provide antiretroviral therapy (ART) to participants who become HIV-positive during a trial was not even on the agenda. At that time, virtually no one in the developing world had access to these life-saving drugs. A decade later, global thinking on ART had totally changed; with activists demanding worldwide access to treatment, the costs of drugs plummeted and the question of ART for trial participants became the focus of heated ethical debate.

This period of ethical deliberation coincided with several high-profile controversies surrounding clinical trials in Cambodia and Cameroon designed to test whether the antiretroviral drug tenofovir might serve as an oral HIV prevention pill. Activists staged protests against the studies, maintaining that they did not guarantee adequate health care in case of HIV infection or trial-related injury and questioning the adequacy of the trials’ informed consent process and risk reduction counseling. Although many of the activist claims were inaccurate, these controversies highlighted the lack of consensus in the wider HIV community about exactly what health care trial participants could rightly expect within the context of HIV prevention trials. Eventually, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the International AIDS Society (together with the Bill & Melinda Gates Foundation, which also provided partial funding for both trials) convened global meetings to discuss the ethical and process-related issues at stake. Similar global meetings were convened by the World Health Organization (WHO) in the late 1990s to discuss the broader implications of these ethical dilemmas for HIV vaccine research.

Around this same time, GCM organized a second global consultation on microbicide trials, entitled Rethinking the Ethical Roadmap for Clinical Testing of Microbicides. Sixty-four people from 12 countries came...
together to debate some of the thorniest issues facing the field: Should trials enroll adolescents younger than 18 years old? What is the appropriate ethical line between fair compensation and undue inducement? And what health and prevention services should be provided to individuals who participate in microbicide trials?

This final question formed the crux of an ongoing debate around the appropriate “standards of care” that should be ensured to trial participants. As described more fully in the next section, “standards of care” is a term borrowed by ethicists from the medico-legal context to refer to the diagnostic, prevention, and treatment services offered to participants in clinical trials. As applied to the question of HIV prevention trials, debates over standards of care have largely focused on the narrow question of whether trial sponsors and investigators have an ethical obligation to provide access to ART for participants who become HIV-positive during a trial. Between 1998 and 2003, for example, UNAIDS hosted at least five separate consultations to solicit input on this question.a

The issue of standards of care as applied to HIV prevention trials, however, is actually far broader. Focusing only on HIV-related care and treatment—and then even more narrowly on access to ART—does a disservice to the complexity of women’s health needs within the context of microbicide trials. One of the advocacy agendas of GCM has been to focus attention on the full range of health and social needs that participants face during clinical research. GCM has also worked hard to forge consensus, especially among civil society actors,

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a The report from the 2003 consultation concluded that “…there is now broad though not unanimous agreement among sponsors of HIV vaccine trials that ART and a clinical care package should be provided to those who become infected during the conduct of a trial.”
Consensus Points on Access to Treatment and Standards of Care in Microbicides Trials

1. Clinical trial sponsors and researchers have a responsibility to ensure appropriate care for any negative health consequences that participants experience as a direct result of trial participation.

2. People who seroconvert during the course of a microbicide trial should be assured access to high quality HIV care, including antiretroviral treatment (ART) when it is needed.
   - Trial sponsors and donors should commit to assuring the availability of such care either directly or through explicit and durable partnerships with other care providers. Such agreements should be formalized in consultation with relevant stakeholders and trial communities before a trial starts.
   - There is no consensus among ethicists as to whether the provision of ART to those who seroconvert during a microbicide trial is ethically obligatory, or “morally praiseworthy” but not mandatory. Nonetheless, we call on the wider microbicides community to ensure access to ART based on ethical aspirations and existing social and political realities.
   - UNAIDS or another such body should convene a task force of clinicians, people living with HIV/AIDS, advocates, health economists, legal and insurance experts, and entities with relevant experience (such as Pharm Access and Médecins Sans Frontières) to develop and evaluate concrete mechanisms for operationalizing ART access for those who seroconvert during microbicide trials, recognizing that they may not need ART for many years into the future.

3. Researchers and sponsors, in collaboration with local and national health authorities, should use microbicide trials as an opportunity to strengthen and improve local standards of care. The minimum objective should be to “ratchet up” care in a stepwise, sustainable fashion to reduce global disparities in access to health care.

4. Explicitly defining each site’s standard of care must be a mandatory part of trial planning. Negotiations should include agreement with stakeholders, including relevant community and/or civil society groups, on the package of prevention services provided to

about what constitutes a reasonable package of care, given the needs and rights of trial participants and host communities, and the competing demands on research funds. Finding this balance is the hard work of ethical reasoning.

As part of this effort, GCM and allied groups issued Consensus Points on Access to Treatment and Standards of Care in Microbicides Trials. This statement emerged from a process of reflection and debate among researchers, advocates, and GCM Steering Committee members over two days in May 2005. The document outlines the minimum that advocates feel researchers should guarantee to participants in microbicide clinical trials (see Box 1).

Significantly, while addressing the issue of access to ART, the document also addresses issues such as access to sexual and reproductive health care, and the need to negotiate durable care arrangements prior to the initiation of a trial.

The consensus document became the foundation for GCM advocacy on this issue and raised the question of how well the field was doing in terms of meeting the expectations outlined therein. To what extent did conditions on the ground conform to the aspirations of advocates or to the various ethics guidance documents that informed the field? With this question in mind, GCM embarked on an exercise in 2006 to map the standards of care and prevention provided to participants in late-stage microbicide trials. The goal of the exercise was four-fold:
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.

To better understand the factors that inform care-related decisions at trial sites.

To explore the microbicides field’s progress toward achieving the ethical aspirations laid out in key ethics guidance documents.

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. Frequently, ethics deliberation in international fora proceeds with little connection to the daily realities of trial participants or the challenges of implementing trials. Yet it is the hundreds of decisions, both large and small, that go into the design and implementation of a protocol that contribute to defining how successfully ethical aspirations are achieved in a trial. Should researchers screen participants as well as on what other care will be ensured either through direct provision or through effective referral mechanisms.

- Referral arrangements should be formalized in writing. Researchers and/or trial sponsors should work to ensure that adequate care is actually received through monitoring and support programs for participants (e.g., transportation, accompaniment programs, etc.).

- Microbicide trials have a special obligation to attend to the sexual and reproductive health needs of participants, including offering direct provision of safe, appropriate contraception for trial participants. Avoidance of unwanted pregnancy will also improve trial power through participant retention.

5. Trial participants should have preferential access to any test product that is shown to be effective. Although ensuring immediate access is complicated by regulatory, manufacturing, and licensing issues, researchers and donors should actively seek to accelerate access to product post-trial through Consensus Points on Access to Treatment and Standards of Care in Microbicides Trials implementation of observational/introductory studies and negotiation with host country governments and product sponsors.

In addition, the Global Campaign for Microbicides commits itself to:

1. Advocate relentlessly for the right of trial communities to have preferential access to any product proven safe and effective, while being completely candid with communities about the likely timeframe of this access.

2. Emphasize in our advocacy the importance of other aspects of standards of care—especially sexual and reproductive health care and the prevention package offered to participants—in addition to HIV care and access to ART.

3. Advocate for the right of host communities and countries to have an authentic voice in decisions around trial-related matters, including negotiations of fair benefits.

4. Work to increase research and ethics literacy among advocates and host communities.

b 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).
for cervical cancer? If abnormalities are found, how and by whom should they be addressed? How do you balance a higher level of care for some with more sustainable care for many?

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.

Mwanza, Tanzania—home to the Microbicide Development Programme’s (MDP) Tanzania study site.

The Unkhanyakude District in rural KwaZulu Natal, South Africa, the location of one of the MDP’s trial sites.
2.0 History and Background on Standards of Care

The term “standards of care” originally derived from law and refers to physicians’ professional and legal obligation to provide the best available medical care to their patients.\textsuperscript{10} Within the context of malpractice law, the customary practices of medical colleagues in the same community define the boundaries between acceptable and unacceptable care. Patients who receive less than the reigning standards of care can sue their provider for “malpractice.”\textsuperscript{11}

Over the last decade, the concept of standards of care has migrated into the general discourse on research ethics. Within the context of clinical trials, ethicists have used standards of care to refer to two different but related notions: the general package of health and prevention services offered to individuals who participate in trials, or more specifically, the treatment or care provided to individuals in the control group of a trial. With respect to HIV prevention trials, it also refers to the package of HIV prevention services and counseling received by trial participants to help them remain HIV-negative. For the purposes of this report, we adopt the definition put forward by the Nuffield Council on Bioethics, a UK-based body specializing in research ethics, that defines “standard of care” as “the nature of the care and treatment that will be provided to participants in research.”\textsuperscript{12} We also agree there is a need to acknowledge a broader concept of standards of care that includes what is available outside the trial context in a community (as per Shapiro and Benatar, see Section 2.3).

“Standards of care” as a concept, however, remains contested, largely because the word “standard” itself is ambiguous. It can mean the prevailing standard—as in what exists—or it can refer to a normative standard—what should exist. Academic medicine distinguishes between what doctors do and what science confirms is best practice. The customary practice that exists in any particular location may or may not conform to “best practice,” as defined by a clinical trial or other metric of evidence-based medicine.\textsuperscript{13}

Moreover, the customary practice of physicians varies widely according to provider knowledge, comfort, training, and belief; local resources; and ability of the patient to pay. What may be standard practice in Amsterdam, for example, may not be the standard in Abuja. Even normative standards can vary because different communities of professionals can reach different conclusions about the implications that a body of evidence should have for the practice of medicine. National guidelines and standards vary significantly among countries, even among systems of medicine in similarly wealthy countries. Until recently, physicians in the United Kingdom, for example, had different practice standards for treating ovarian cancer than US physicians because of differing interpretations of the evidence.\textsuperscript{14} It is little wonder then that deliberations on “standards of care” have been grist for disagreement and debate.

2.1 What Do Ethics Guidance Documents Say?

As stated, ethics guidance addresses standards of care within two contexts: (1) general expectations regarding provision of health care for participants in trials, and (2) specific recommendations regarding provision of services to participants in the control group of a study.

Ethical views on the obligation of investigators and sponsors to provide general health care to clinical trial participants are currently in flux (see Box 2). Traditional thinking and some guidance documents maintain that investigators and study sponsors are only legally and ethically responsible for providing or paying for that care which is necessary for the safe conduct of the research project. For example, [Quote: International Ethical Guidelines for Biomedical Research Involving Human Subjects, Council for International Organizations of Medical Science (CIOMS)]:

External sponsors are ethically obliged to ensure the availability of health-care
Guidelines on Required Provision of Health Care for Participants in Clinical Trials

The Declaration of Helsinki, World Medical Association (2000)
• No specific mention of HIV prevention trials.
• No specific obligations regarding provision of medical care during research.
• General statement of obligation, open to strong and weak interpretations (Paragraph 10: “It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.”).

International Ethical Guidelines for Biomedical Research Involving Human Subjects, Council for International Organizations of Medical Science (2002), Guideline 21
• The ethical obligation of external sponsors is to provide health care-related services.
• Must provide health care services that are essential to the safe conduct of the research.
• External sponsors are ethically obliged to ensure the availability of treatment for subjects who suffer injury as a consequence of research interventions.

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

• Endorses Guidance Point 16 of the UNAIDS vaccine guidance document.
• “We conclude that where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered is the best available intervention as part of the national public health system for that disease.”

services that are essential to the safe conduct of the research.15

Although sponsors are, in general, not obliged to provide health-care services beyond that which is necessary for the conduct of the research, it is morally praiseworthy to do so. Such services typically include treatment for disease contracted in the course of the study. It might, for example, be agreed to treat cases of an infectious disease contracted during a trial of a vaccine designed to provide immunity to that disease, or to provide treatment of incidental conditions unrelated to the study.16

However, many researchers, activists, and ethicists have begun to challenge this view, arguing that there is a moral obligation to provide some care beyond that required by the study, especially in resource-poor settings where weak health care infrastructures and poverty make it particularly difficult for people to access even basic health care services.17

Given the lack of clear consensus on this point, many ethicists have looked to “process-oriented” solutions. The Nuffield Council argues in their document, The Ethics of Research Related to Healthcare in Developing Countries:

We recommend that before research begins agreement should be reached about the standard of care that should be provided to participants in research who already have or who develop diseases other than the diseases being studied. We conclude that the minimum standard of care that should be offered is the best intervention available as part of the national public health system.”18
2.2 Ethics Controversy

In the late 1990s, disagreement over the level of care owed participants erupted into bitter controversy within the context of trials funded by the US Government to test the effectiveness of novel strategies to prevent mother-to-child transmission of HIV. A trial in the United States had recently demonstrated that an intensive regimen of oral and intravenous provision of the drug zidovudine, or AZT (formerly azidothymidine), could reduce perinatal transmission of HIV by 67 percent.19,20 This regimen, known as ACTG 076, quickly became the “standard of care” in the United States.

The 076 regimen, however, was difficult if not impossible to implement in most developing world settings. It required pregnant women to begin drugs in the second trimester, long before many women in Africa and Asia were in contact with the health system, and it required intravenous administration of AZT during childbirth. These facts, together with the high cost of AZT, spurred researchers to test alternative drugs and regimens that might be more feasible.

The controversy emerged from the decision of researchers to test the simplified regimens against a placebo rather than against the complex regimen of AZT that had become standard practice in the United States. Critics such as Marcia Angell, the executive editor of the New England Journal of Medicine, and Peter Lurie and Sydney Wolfe of Public Citizen (a consumer protection organization in the United States) argued that failure to provide the US standard of care amounted to a dangerous double standard of research.

Agreement should be reached before research begins about the standard of care to be provided to subjects.

Any proposal for care of a lower standard must be justified to the relevant research ethics committees.

Ethical Considerations in Biomedical HIV Prevention Trials, UNAIDS/World Health Organization (2007)

- Participants who acquire HIV infection during the conduct of a biomedical HIV prevention trial should be provided access to treatment regimens from among those internationally recognized as optimal. Prior to initiation of a trial, all research stakeholders should come to agreement through participatory processes on mechanisms to provide and sustain such HIV-related care and treatment.


- “Sponsors and investigators must ensure that treatment and care for HIV infection is provided to participants who become HIV-infected during the course of an HIV vaccine trial.”
- Components of treatment and care for HIV-infected participants are outlined.
- Agreement that “…sponsors and investigators should provide, or ensure access to, high quality treatment and care for participants who become infected during the course of an HIV preventive vaccine trial, including ART [antiretroviral therapy].”
- Agreement that “…persons who are identified as HIV-infected at screening for participation in a trial should be referred to existing health care services, with the understanding that there will be progressive implementation of a programme of state-supported ART.”
- “Prior to the initiation of any trial sponsors should ensure that resources are contributed towards the treatment and care of trial participants.”
ethics.\textsuperscript{21,22} In defense of their position, they cited Paragraph 29 of the \textit{Declaration of Helsinki}, which states that a new intervention must be tested against “those of the best current prophylactic, diagnostic, and therapeutic method, unless no proven intervention exists.”\textsuperscript{23} Others, including a number of prominent researchers and practitioners in developing countries, argued that it made little sense to provide interventions that countries could not sustainably implement and that context was indeed ethically relevant.

At issue in this case was that the frame of reference should be used to define “the best current” intervention. Does best current refer to the best treatment available anywhere in the world, or is context relevant? The 076 controversy pitted those who argued for one “uniform standard” against those who argued

\begin{boxedtext}
\textbf{Guidance Related to the Use of Placebos in Clinical Trials}

\textit{The Declaration of Helsinki, World Medical Association (2000)}

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

\textit{International Ethical Guidelines for Biomedical Research Involving Human Subjects, Council for International Organizations of Medical Science (2002)}

- Guideline 11: “As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an \textbf{established effective intervention}. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or no treatment.”

\textit{The Ethics of Research Related to Healthcare in Developing Countries, Nuffield Council on Bioethics (2002)}

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

\textit{Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, Council of Europe (CETS No. 195) (opened for signature 2005; entered into force 2007)}

- Article 23.2: Research shall not deprive participants of necessary procedures. “…in research associated with prevention, diagnosis or treatment, participants assigned to control groups [shall] be assured of a \textbf{proven method of prevention, diagnosis, or treatment}.”

- “It is expected that a \textbf{proven method of treatment that is available in the country or region concerned be utilised}.”


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

Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries, National Bioethics Advisory Commission (2001)
- Researchers and sponsors should design clinical trials that provide members of any control group with an established effective treatment, whether or not such treatment is available in the host country. Any study that would not provide the control group with an established effective treatment should include a justification for using an alternative design. Ethics review committees must assess the justification provided, including the risks to participants, and the overall ethical acceptability of the research design.

- Participants in both the control arm and the intervention arm should receive all established effective HIV risk reduction measures. The use of a placebo control arm is ethically acceptable in a biomedical HIV prevention trial only when there is no HIV prevention modality of the type being studied that has been shown to be effective in comparable populations.

- 11.1: A vaccine with proven efficacy in preventing infection or disease from HIV does not currently exist. Therefore, the use of a placebo control arm is ethically acceptable in appropriately designed protocols.
- 11.2: Participants in the control arm of future HIV preventive vaccine trials should receive an HIV vaccine known to be safe and effective when such is available, unless there are compelling scientific reasons which justify the use of a placebo.
- 11.2.1: Compelling scientific reasons to use a placebo rather than a known effective HIV vaccine in the research population include:
  - evidence that the HIV vaccine is highly unlikely to be effective against the virus that is prevalent in the research population; and
  - convincing reasons to believe that the biological conditions that prevailed during the initial trial demonstrating efficacy were so different from the conditions in the proposed research population that the results of the initial trial cannot be directly applied to the research population under consideration.
The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method. 

Other well-known guidance documents, however, advance differing perspectives. The CIOMS guidance recommends that participants in the control arm of a trial receive “an established intervention” (as opposed to the best one available), while the Nuffield Council argues that participants should receive a universal standard except in those cases where a universal standard is “not appropriate.” Nuffield provides no criteria for “inappropriate,” but does maintain that in such instances, the minimum provided should be the best treatment available as part of the national public health service. The Council of Europe mandates that participants receive “a proven method of treatment that is available in the country or region concerned.” In sum, the Declaration of Helsinki is the only ethics guidance that proponents routinely interpret as requiring the best intervention proven anywhere as the ethical minimum.

### 2.3 The Debate Comes of Age

Despite the controversy, the perinatal HIV trials continued, and in the end, demonstrated that a single dose of neviripine, an inexpensive antiretroviral drug, could substantially reduce mother-to-child transmission of HIV. This finding had profound implications for public health and temporarily diffused tensions around standards of care. Eventually, debate matured beyond black and white distinctions—between the best care anywhere and the inadequate care that existed in many of the settings that hosted HIV prevention trials. Ethical opinion began to converge on a middle ground that posited that sponsors have an obligation to “ratchet up” local care even though they may not be able to achieve state-of-the-art care in the short term. As South African ethicist, Solomon Benatar, and his colleague, Katharine Shapiro, observe:

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

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

It is in this spirit that GCM pursued the standards of care mapping exercise described in this report.

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World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended most recently by the 52nd WMA General Assembly, Edinburgh, Scotland, 2000. This is an amendment in the form of a footnote to Paragraph 29, approved by the WMA General Assembly, Washington, DC, 2002.
3.0 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, 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. For the purposes of collecting data, we developed a semi-structured interview guide that covered the ten domains listed in Box 4.

In selecting sites to visit, 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® (a candidate microbicide), 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 was also in attendance at the consultation described in the next paragraph.

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.

### Standards of Care Survey Domains

Throughout the course of this exercise, questions from the following ten domains were posed to international investigators, local investigators, and local study staff.

1. HIV prevention services
2. Study-related health care (sexual and reproductive health care)
3. HIV care and treatment
4. Capacity-building and community involvement
5. Non-study related care
6. Care for research-related harms
7. Post-trial access to product
8. Male partner involvement
9. Role of sponsors and funders
10. Staffing
to serve as a standards of care advisory group and attend a two-day consultation in Johannesburg, 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 marked with ➔ and HIGHLIGHTED IN BLUE BOLDFACE are “consensus recommendations” that emerged from the consultation. The recommendations marked with ★ and HIGHLIGHTED IN GRAY BOLDFACE are “authors’ recommendations.” Authors’ recommendations represent ideas that emerged in the aftermath of 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 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 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. WHO launched its “3 by 5” initiative in 2003, advocating 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.

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.
4.0 Description of Trials and Sites Visited

At the onset of this mapping, six organizations were conducting effectiveness trials of five different microbicide candidates and one of the diaphragm (see Table 1). At the time of writing, only two of the six studies were ongoing—the HIV Prevention Trials Network (HPTN) 035 study and the MDP 301 study. This section describes the studies reviewed, the organizations charged with implementing the trials, the trial designs, and the settings of the various trial sites. Appendices III and IV provide additional information on the organizations that sponsored and funded these trials, as well as a table summarizing similar information for all of the trials and sites included in the mapping exercise.

**Table 1: Studies and Sites Included in the Standards of Care Mapping Exercise**

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

CONRAD, Contraceptive Research and Development; DSMB, Data Safety Monitoring Board; FHI, Family Health International; HPTN, HIV Prevention Trials Network; MDP, Microbicides Development Programme; MWAMKO, Mwanamke Amua Kuhusu Maisha Yaiko (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 study product at a 2% concentration.
4.1 Contraceptive Research and Development: Cellulose Sulfate

Contraceptive Research and Development, or CONRAD, is a US-based, nonprofit organization funded by the US Agency for International Development (USAID) and the Bill & Melinda Gates Foundation. Before it prematurely closed its study in January 2007 at the recommendation of its Data Safety Monitoring Board (DSMB) (see Box 5), CONRAD was implementing a Phase 3 trial of the candidate microbicide Cellulose Sulfate at five sites: Cotonou, Benin; Durban, South Africa; Kampala, Uganda; and Bangalore/Bagalkot and Chennai, India. For the purposes of this mapping exercise, we visited the study site in Cotonou, Benin.

Site Description: Cotonou, Benin

Located in French-speaking Benin, Cotonou is a large port city on the west coast of Africa. The prevalence of HIV in Benin remains low at 1.8 percent and is largely contained within high-risk populations of women with multiple partners.27 At the time of our visit, HIV prevalence among women participating in the study, however, was 27 percent, far above the national level.e

The study enrolled two sets of women: one that worked openly in brothels (les affichées), and a second group that did not necessarily self-identify as sex workers but engaged in sex work clandestinely (les clandestines). The latter lived with their families and worked at night in local clubs, bars, and hotels. Because these women were not organized but worked individually, they seldom frequented the health and social services available to sex workers. This put them at higher risk than the women working in brothels. The brothel-based sex workers were mainly foreigners (predominately Nigerian and Ghanaian), were highly mobile, and were difficult to follow. The les clandestines on the other hand were largely from Benin and relatively easier to follow up. Study participants were at least 18 years old and had an average of at least three sexual acts per week and at least three sexual partners in the three months preceding their enrollment in the study.

The main CONRAD research clinic sat within the sexually transmitted infection (STI) reference clinic for the national AIDS control program, Dispensaire Pour les Maladies Sexuellement Transmissible (referred to from this point on as DIST), on the site of a local fee-for-service community hospital providing primary health care to the general population. Services at DIST were targeted especially to women with multiple sexual partners (and their partners) and available to anyone free.

The Case of Cellulose Sulfate

Typically, only one in five candidates entering effectiveness trials makes it to market as a new drug. As the case of Cellulose Sulfate (CS) illustrates, frustrating setbacks are inherent in the process of conducting cautious, ethical research in the face of a devastating and fast-moving pandemic.

Contraceptive Research and Development’s (CONRAD) Data Safety Monitoring Board (DSMB) met in January 2007 to review preliminary data from the Phase 3 trial of CS, a candidate microbicide. They recommended that the trial, already underway in Benin, India, South Africa, and Uganda, be discontinued because emerging data hinted that CS might be increasing HIV risk among some participants. Erring on the side of caution, the DSMB monitoring Family Health International’s CS trial in Nigeria also immediately recommended discontinuation, even though the Nigerian data did not indicate increased risk.

In the final analysis, CONRAD’s CS results showed no statistically significant difference between the control and active arms of the trial—but a per-protocol analysis did suggest increased susceptibility among women using CS.28 The only definitive conclusion drawn from the CS trial is that the product does not reduce risk of HIV infection.
of charge. Since the early closure of the CS trial (see Box 5), both study clinics have seen a reduction in staff and services but remain open due to an influx of new funding from the national AIDS control program and two international nonprofit organizations.

At the time of our visit, the local care environment in Cotonou consisted of a poorly resourced, fee-for-service public health system. Those in Cotonou had to pay for almost all preventive and curative services (including all medicines), except for HIV and STI care, assuming they were able to access it. TB treatment was also free, although at the time of our visit, patients were required to pay for TB diagnosis (this service is now also free of charge).

4.2 Family Health International: SAVVY® and Cellulose Sulfate

FHI is an international, nonprofit organization based in the United States with a long history of conducting research and managing health and HIV-related programming in more than 60 developing countries. With funding from USAID, FHI implemented two Phase 3 trials of the candidate microbicide, SAVVY® (C31G), one at two sites in Ghana (Kumasi and Accra), and another at two sites in Nigeria (Lagos and Ibadan). In November 2005, the trial’s DSMB halted the Ghanaian study because the HIV incidence encountered was too low to be able to evaluate the effectiveness of SAVVY®. In August 2006, FHI closed the Nigerian SAVVY® study after an independent data monitoring committee determined that the trial was unlikely to find a protective effect of SAVVY® if it continued.

FHI investigators also implemented a Phase 3 trial of CS at two sites in Nigeria (Lagos and Port Harcourt). In January 2007, FHI’s DSMB made the decision to prematurely stop their CS trial (see Box 5) as well.

As described more fully in Section 3.0, we did not visit FHI trial sites as part of this exercise. The SAVVY® trial sites in Ghana and Nigeria had closed by the time of our field visits, and we made the decision not to visit the CS Nigeria sites for security reasons. Therefore, site-specific data for these trials are incomplete and not fully comparable to those where site visits were conducted. Nonetheless, we include information gathered from the Ghana and Nigeria sites here because we feel it is important to present the broadest possible range of issues and lessons learned. Information on the FHI trials included in this report is based on telephone interviews with the international principal investigators—and in the case of the CS trial, the country-level principal investigator—and a comprehensive desk review, including a review of site-specific documents. The country-level investigator for the CS study in Nigeria also attended the standards of care consultation, at which time we were able to gather more information about the study. Where all sites are compared in table format, each FHI site is clearly marked as “Site Not Visited” to alert the reader to the limitation of the contextual information we were able to obtain for these examples.

For both the SAVVY® and CS studies, the study populations consisted of sexually active women at high risk of acquiring HIV—defined as having intercourse, on average, three times per week and having more than one sexual partner in the three months preceding their enrollment. At the FHI CS trial site in Lagos, Nigeria, most women who participated in the study supplemented their income with some form of transactional sex. The women did not work in established brothels, but mostly operated out of bars and trailer parks.

For both the FHI SAVVY® and CS studies, participants visited main study clinics for screening, enrollment, and final visits but attended monthly visits at outreach posts that

“Lagos is a vast place and it’s hard to get around; no doubt that it’s a deterrent [for participants to come to outreach centers]. In Nigeria we had a good number of university students [participating in the study and] market women, same for Ghana. Either market women or they would go out at night but during the day they would sell things at market. In Ibadan we recruited at the university and bars and clubs at night.”

—INTERNATIONAL INVESTIGATOR, US/NGERIA
had limited clinical facilities. At the time of study design, the UNAIDS report estimated national HIV prevalence rates at 3 percent for Ghana and 5.8 percent for Nigeria.\footnote{29}

4.3 Microbicides Development Programme: 0.5% and 2% PRO 2000 Gel

The MDP is a public-private partnership funded by the UK Medical Research Council (MRC) and the UK Department for International Development.\footnote{30} At the time of writing, there were five active research sites currently following women in their Phase 3 trial of the candidate microbicide PRO 2000/5 (known simply as PRO 2000): three in South Africa (Durban, Johannesburg, and at the Africa Centre in Umkhanyakude District, KwaZulu Natal), and one each in Mwanza, Tanzania, and Masaka, Uganda. As part of the standards of care mapping exercise, our research team visited the MDP sites in KwaZulu Natal, South Africa, and Mwanza, Tanzania.

Site Description: Umkhanyakude District, KwaZulu Natal, South Africa

The MDP’s Africa Centre site was situated in a rural and periurban area of Umkhanyakude District, KwaZulu Natal, South Africa. Overall, KwaZulu Natal has the highest HIV prevalence in South Africa—21.5 percent among residents (those who permanently reside in the area), and even higher, 31-41 percent, among non-residents (those who do not live in the area permanently but regularly visit).\footnote{31} Among the population of women ages 25-29 accessing primary care facilities in the study area, HIV prevalence is 50 percent.\footnote{Per data made available by study staff during our site visit.}

Women participating in the MDP study were those 18 years and older who were sexually active and who reported having intercourse at least once in the three months preceding their enrollment. Recruitment for this study was ongoing at the time of our visit, with most women recruited from public health clinics. These women were generally single or without a partner at home. Study staff reported that a fair number of women in the area had steady partners but continued to live at home due to the prohibitively high cost of marriage. Despite the low number of women cohabitating with a partner, most women suffered from a high rate of intimate partner violence.\footnote{32}

The MDP study was implemented in partnership with the Africa Centre for Health and Population Studies (Africa Centre), an established center for research funded by the Wellcome Trust and the site of the local PEPFAR grant to provide HIV care and ART. The three MDP study clinics were located in Mtubatuba, KwaMsane, and Madwelani in Umkhanyakude District, KwaZulu Natal. All were run out of portable buildings situated a few feet from Department of Health (DoH) PHCs, allowing for strong, organic links between the study and the DoH clinics.

Since independence, South Africa has made free health care for all citizens a priority, and at the time of our visit, primary health services were widely available and within reach. Access to secondary and tertiary facilities, however, was at times problematic due to long distances, time constraints, and transportation expense. Local DoH clinics were well-stocked, and providers well-trained, but major staffing shortages and building limitations at all levels meant long waits and hurried care by overworked providers. Study staff reported that community-based organizations (CBOs) tended to come and go in the area, leaving a distinct gap in social services.

Site Description: Mwanza, Tanzania

Tanzania is one of the poorest countries in sub-Saharan Africa, with a longstanding HIV epidemic that appears to have stabilized in the general population but continues in high-risk groups. At last report, the overall national HIV prevalence rate for Tanzania was 6.5 percent.\footnote{33} Mwanza, the location of the MDP study site in Tanzania, is the country’s second largest city, sprawling along the shores of Lake Victoria.

The study population consisted of two groups: a more mobile population of women 16 and older working in bars, restaurants, and hotels, and mamalisches, women who tended to be older and more stable and who prepared food for sale and/or worked in traditional bars preparing and selling local beer. Many of these...
women did not identify as sex workers but typically engaged in some form of transactional sex to supplement their incomes. Many had primary partners.

The study, known as MWAMKO (*Mwanamake Amua Kuhusu Maisha Yako* in Kiswahili, translated to “Women decide your life” and “Wake-up” in English), was run from the offices of the African Medical Research Foundation (AMREF). AMREF has been engaged in research in the area for many years in partnership with the London School of Hygiene and Tropical Medicine and the UK National Institute for Medical Research. Study activities took place in eight mobile clinics set up once weekly for a half-day in guesthouses and hotels close to various clusters of participants, allowing for easy access to study clinics.

In general, the population in Mwanza had difficulty accessing local health services because of the cost to the individual paired with an overburdened, under-resourced health system. Almost all services and medicines were provided at cost to patients (except HIV and STI care), and waits for care were reported to be long. There were a number of nongovernmental and community-based organizations in the area, many of which were faith-based, that were available to provide some support services to the community.

### 4.4 The Population Council: Carraguard® Gel

The Population Council, an international, nonprofit, nongovernmental organization (NGO) headquartered in New York, has been involved in microbicide development since the late 1980s. With funding from USAID and the Bill & Melinda Gates Foundation, the Council completed a Phase 3 trial of Carraguard®, a non-contraceptive vaginal gel designed to protect women from HIV. Investigators implemented the study in three South African sites: Gugulethu, Soshanguve, and Durban. The trial demonstrated that Carraguard® had a good safety profile but failed to demonstrate any protective effect against HIV. As part of this exercise, the GCM team visited the study sites in Gugulethu and Soshanguve.

**Site Description: Gugulethu, South Africa**

Gugulethu is a township in Nyanga District of Cape Town, South Africa. Nyanga is one of the oldest migrant worker communities in South Africa, with most of its residents speaking Xhosa as their first language. The study population included sexually active women, ages 16 and older (later changed to ages 16–40 per protocol amendment), who had at least one act of sexual intercourse in the three
months preceding their enrollment in the trial. While HIV prevalence in the Western Cape hovers at just more than 15 percent, the overall HIV prevalence in Gugulethu is estimated at 29 percent, representing a concentration of the epidemic in this community. At the time of our visit, HIV prevalence among the women from Gugulethu volunteering for screening was 17.5 percent.

The study operated a single site that contained a clinic, administrative offices, and a study laboratory. The study clinic, Empilisweni (“Place of Health”) Center for Wellness Studies, operated in partnership with the University of Cape Town. The study clinic sat within the Uluntu Community Center, which housed other NGOs and a human papillomavirus (HPV) research study.

Although governmental denial at the highest national levels has greatly hampered access to HIV prevention, treatment, and care in South Africa, the local and provincial governments of Western Cape Province and the City of Cape Town have moved forward independently to provide services. Despite social and economic problems in Gugulethu Township, residents did have access to high quality, integrated health services free of charge at eight PHCs that included sexual and reproductive health services, HIV/ART care and treatment, and management of other acute and chronic health problems. Services were overburdened and waits were long, but care was accessible.

Site Description: Soshanguve, South Africa

The periurban district of Soshanguve is located approximately 30 minutes outside of Pretoria, South Africa, and is home to just less than 450,000 residents. During our visit in late 2006, unemployment was high in the township, and HIV/AIDS-related stigma and domestic violence were commonly reported problems. HIV prevalence was more than 30 percent among the overall population of Gauteng Province and 24 percent among the population of women that volunteered for study screening.

The population of women enrolled in the study were sexually active women, ages 16 and older (later changed to ages 16–40 per protocol amendment), who had at least one act of sexual intercourse in the three months preceding their enrollment. The study site in Soshanguve operated in a former stand-alone district PHC refurbished with research funds to provide administrative, laboratory, and clinic space. Named Setshaba, the study clinic operated in partnership with the Medical University of South Africa.

Local PHCs in this region, as in Cape Town, provided a complete range of sexual and reproductive health and primary health care free of charge, including HIV care for opportunistic infections (OIs); however, shortages of space and trained providers limited quality of care. At the time of our visit, initiation onto ART and the dispensing of drugs were available only at one hospital, and distance and cost of transport were barriers to accessing both. Beyond these government-run services, there were few NGOs in the area providing social support to people with HIV.
4.5 HIV Prevention Trials Network
HPTN 035: 0.5% PRO 2000 Gel and BufferGel

The HPTN was a global clinical-trials network that developed and tested the safety and efficacy of non-vaccine interventions to prevent the transmission of HIV. Funded by the Division of AIDS of the National Institute of Allergy and Infectious Diseases of the US National Institutes of Health (NIH), the HPTN developed and implemented HPTN 035 through June 2007. In 2007, the NIH re-competed all of its clinical trial networks and formed a separate stand-alone Microbicide Trials Network (MTN). Since that time, HPTN 035 has been supported and coordinated by the MTN, although most aspects of the study implementation have remained unchanged.

HPTN 035 is a Phase 2/2b expanded safety and effectiveness study of the microbicide candidates PRO 2000 and BufferGel. At print, MTN is implementing this study at six sites in Africa and one in the United States: Harare, Zimbabwe; Blantyre and Lilongwe, Malawi; Lusaka, Zambia; Durban and Hlabisa, South Africa; and Philadelphia, USA. For this exercise, we visited the HPTN 035 site located in Harare, Zimbabwe.

Site Description: Harare, Zimbabwe

Zimbabwe has been hard hit by economic and political challenges, high unemployment, and soaring inflation. National HIV prevalence is around 20 percent, and was closer to 30 percent among the women who had volunteered for the study at the time of our visit.

The study population was comprised of sexually active women between the ages of 18 and 35 who reported having had vaginal intercourse at least once in the three months preceding their enrollment in the study. Women were recruited from family planning clinics, postnatal clinics, STI clinics, and community-based locations, or referred from other local research projects and health and social service providers.

The University of Zimbabwe-University of California, San Francisco (UZ-UCSF) Collaborative Research Programme implemented the HPTN 035 study in one periurban and one urban site near Harare. Administrative offices were located in the government’s Pariyenatwa Hospital and Outpatient Family Health Clinic complex in Harare, and the study clinics, Seke South and Spilhaus, were located in nearby communities. Study clinics were stand-alone structures co-located with government-supported health and social service facilities.

“There’s high level corruption in Zimbabwe. But here is a sister running an OI clinic and getting paid [very little per] month. She could run an OI clinic out of her house if she was corrupt but she is keeping the ARVs locked every night because she is true to her cause. If that was true at the higher levels, this would be a different country.”

—INVESTIGATOR OF RECORD, ZIMBABWE

Although Zimbabwe previously had one of the best health care systems in the region, services have deteriorated in the past decade, and at the time of our visit, patients had to pay for almost all care. Staff shortages, fuel shortages, and drug stockouts exacerbate problems. Access to care and treatment for HIV was increasing, but services were overwhelmed. The waiting list for ART was long, and the required baseline testing was prohibitively expensive. There were some NGOs and CBOs that provided services in the area, but they too tended to be overwhelmed and under-funded. Social welfare was available for those who were indigent and could not pay for care; however, grants were administratively complex and had to be renewed yearly.

4.6 Women’s Global Health Imperative: Methods for Improving Reproductive Health in Africa Diaphragm Study

The Women’s Global Health Imperative, or WGHI, is a global research center that conducts collaborative research and training related to HIV/AIDS, gender, reproductive health, and safe motherhood. At the time of this study, WGHI was based at the University of California,
San Francisco, although it recently moved to RTI International, an independent research institute based in North Carolina. At the time of our visit, WGHI had just concluded its Phase 3 trial of the Ortho All-Flex® latex diaphragm and Replens® lubricant gel in Harare, Zimbabwe, and Durban and Johannesburg, South Africa (see Box 6). As part of this exercise, we made a visit to the study site in Harare, Zimbabwe.

Site Description: Harare, Zimbabwe

WGHI implemented the Methods for Improving Reproductive Health in Africa (MIRA) diaphragm trial at two sites in the nearby Harare suburbs of Chitungwiza and Epworth, via the same collaborative research project (UZ-UCSF) that implemented the HPTN 035 study and within the same economic and health care environment (see Section 4.5 above).

The study population consisted of women ages 18–49 with an average of at least four sex acts per month, recruited from general health clinics and CBOs and through advertisements in the local media.

“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

Results of the Methods for Improving Reproductive Health in Africa Trial

Results from the Methods for Improving Reproductive Health in Africa (MIRA) trial were published in *The Lancet* in July 2007.39 The HIV incidence in the intervention group was 4.1 percent per 100 woman years and was 3.9 percent in the control group. [Note: the term “person-years” is a convention from epidemiology that allows researchers to annualize estimates of infection from individuals followed up for different lengths of time.] Despite the rigorous promotion of condoms to both groups, the proportion of women using condoms was significantly lower among women in the intervention group than in the control group (54 percent versus 85 percent of visits). The investigators observed that although the diaphragm appeared safe, no protective benefit against HIV infection was found when the diaphragm and lubricant (non-microbicide) gel were provided in addition to the HIV prevention and risk reduction packages and condoms given to women in both groups.

The investigators also noted that, despite the much lower use of condoms in the intervention group, there was no increase in HIV infection, which suggested that diaphragm use might have compensated for the difference in condom use.

The disappointing results of this trial exemplify many of the difficulties and unanswered questions faced by all HIV prevention trials. Rigorous provision of condoms and HIV risk reduction packages make it harder to show a small difference between the intervention and the control arm. Furthermore, because both condom and diaphragm use are self-reported, figures may be under- or over-estimated, thus clouding the results. Finally, although the high rates of condom use reported during the study are encouraging, they may not be sustainable in people’s real life situations, now that the trial is over and the need for woman-controlled methods remains as urgent as ever.
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 OIs 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.

During actual study implementation, many researchers and study personnel went considerably beyond the care stipulated in protocols or SOPs to help fill obvious care-related gaps, often using their own time and money to do so. But many also felt conflicted and uncertain about the nature and extent of their obligation to provide care for trial participants or their communities—an issue that researchers wrestle with personally and also collectively as a field. Will the extra resources required for care hamper the conduct of research, or create expectations that cannot be sustained without the infusion of research-related resources? What are the justifications for improving the standards of care in trial settings and communities? What are the boundaries between improving care and creating undue inducement to participate?

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 or not the trial ensured future provision of ART for women who seroconverted during the trial.

As stated, we observed major variations in the challenges that different sites faced in providing
We then end with an overview of other findings of the standards of care mapping exercise, outlining how various studies managed care-related issues, care for research-related harms, and discussing the key variations observed across studies and sites. The findings are organized according to the domains explored as part of this mapping. We begin with HIV prevention services, followed by a discussion of other counseling and support issues that were identified throughout the course of the project. Next we review study-related care issues including STI screening and care, cervical screening and care, pregnancy and contraception, and HIV care and treatment. We follow this with a discussion of management of partner-related care issues, non-study related care, in-country capacity building, community involvement in care-related issues, care for research-related harms, and post-trial access to study products. We then end with an overview of other overarching issues that were also identified.

5.1 HIV Prevention Services

All of the trial sites reviewed for this exercise provided a baseline prevention package that included risk reduction counseling, HIV counseling and testing (referred to here as voluntary counseling and testing, or VCT), and promotion and provision of condoms. The variations that we observed across sites included the counseling approaches; whether or not the condom negotiation skills were taught; practices regarding the female condom; and which staff provided the counseling services in question.

Ethicists and researchers generally agree that “appropriate risk-reduction counseling and access to prevention methods should be provided… with new methods being added as they are discovered and validated.” However, what constitutes “appropriate” and how to establish the “validity” of different interventions is less clear. Some ethics guidance documents mention counseling as a requirement; some specifically state that risk reduction counseling should be provided to participants; and others assert that all “…research projects must ensure that effective means of prevention for HIV and STI transmission that would be practically achievable as a standard of care in the local setting are reasonably accessible by all people who are screened or enrolled.”

Overall, the risk reduction counseling that sites provided was of high quality, and concerns over potential conflicts of interest that might arise from researchers directly providing risk reduction counseling appeared to be unfounded (see Section 5.1.1 for further elaboration). Still, the various counseling approaches that studies employed offer potentially valuable lessons for future trials and warrant further evaluation.

5.1.1 Risk Reduction Counseling

Risk reduction counseling is a proven and essential HIV prevention strategy known to enhance knowledge of HIV/STIs and skills for condom use and other safer sex practices. From protocol reviews and site visits, we

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CASE STUDY 1

Provision of Condoms in Cotonou, Benin

In Benin, women enrolled in the trial were given a number of condoms per visit equal to the number of sex acts reported since their last visit, while those not in the trial received a pack of 48 per month. Some participants with 5–15 partners per night received >120 condoms at a time. Since the price of condoms tripled in Cotonou during the course of the study, this became a concern among women as they approached closeout. Staff noted that an increase in the number of reported sex acts was possibly a strategy by women to save gel and/or condoms for post-trial use. After the trial closure, all women in and out of the study continued to receive 48 free condoms monthly, thanks to a new Canadian research project that took over clinic services jointly with the national AIDS control program (Programme Nationale de Lutte Contre le Sida). However, with the premature closure of the trial, the women with multiple partners who were more often in need of specialized health services, received >120 condoms at a month. Some participants tended to be behaviorally lower risk than those in Benin and Tanzania, but government health services and the population were suffering from severe economic and political crises that limited the availability of all goods and services.

The following sections review the specific findings of the standards of care mapping exercise, outlining how various studies managed the provision of care and prevention services, and discussing the key variations observed across studies and sites. The findings are organized according to the domains explored as part of this mapping. We begin with HIV prevention services, followed by a discussion of other counseling and support issues that were identified throughout the course of the project. Next we review study-related care issues including STI screening and care, cervical screening and care, pregnancy and contraception, and HIV care and treatment. We follow this with a discussion of management of partner-related care issues, non-study related care, in-country capacity building, community involvement in care-related issues, care for research-related harms, and post-trial access to study products. We then end with an overview of other overarching issues that were also identified.

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Footnotes:

j Both the Declaration of Helsinki (Paragraph 8.18) and CIOMS (Guideline 8, 2002) highlight the importance of informing healthy participants of risk and burdens and minimizing risks when participating in a trial that speaks indirectly to the requirement for counseling.

k 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.”
observed that the risk reduction counseling provided by studies was generally of high quality, especially in comparison to what public facilities were able to offer locally. At trial sites, risk reduction counseling was unlimited in terms of the time allowed and the frequency of visits. Mechanisms to maintain confidentiality were in place, and counselors were well-trained, monitored, and saw a reasonable number of clients per day (see Box 7).

As designated in study protocols, all trial sites offered women information on HIV/STI risk and condom use at screening and enrollment, during quarterly study visits, and at study closing. Additional counseling was available upon request and at any interim visits that may have occurred. Some sites provided risk reduction counseling monthly rather than quarterly, either consistent with their protocol’s designated visit schedule (FHI SAVVY®, FHI CS, CONRAD) or beyond their protocol requirements (HPTN 035, whose protocol called for counseling to be done quarterly, offered counseling at all monthly study visits).

By contrast, due to shortages of human resources, physical space, and time, risk reduction counseling was extremely limited in the public facilities that we visited. Government-run HIV clinics in Zimbabwe, for example, referred all clients to a nearby NGO for HIV-related counseling and psychosocial support. Occasionally, NGO-employed counselors provided counseling onsite at the HIV clinic, but due to lack of space and resources, counseling often took place in hallways or outdoors, with one counselor seeing up to 15–20 clients per day. By contrast, counselors at study clinics saw less than half that number. At one PHC, adjacent to an MDP Africa Centre clinic, an HIV counselor reported seeing 45 clients the previous day. On the same day, at the adjacent microbicide study site, each counselor saw an average of four participants.

Sites also varied in the strategies they employed for counseling. Some sites used standardized counseling scripts, while others used broad guidelines, or tailored messages to specific client needs (e.g., increased risk reduction counseling in the presence of a positive STI result). Others took great pains to work with participants to develop individualized risk reduction plans. Counselors at most study sites advised participants on how to disclose microbicide gel use to partners, and some additionally emphasized the need to involve a woman’s partner(s) in order to successfully implement her risk reduction plan. Some sponsors provided study-wide counseling manuals to direct counseling strategies across all of their study sites.

**Approaches to Risk Reduction Counseling**

- Counselors at the Microbicides Development Programme site at the Africa Centre in Umkhanyakude District of KwaZulu Natal were trained in the standard ten-day South African counseling course in voluntary counseling and testing. They also sat for an exam, performed a mock counseling session with the study’s counseling coordinator, and were observed during their first counseling sessions and then quarterly thereafter to maintain quality control. A study psychologist was available to assist with difficult issues and to provide personal support to the counselors.

- Staff at the Contraceptive Research and Development (CONRAD) Benin site emphasized that everyone on staff provided some risk reduction counseling and education. Peer educators and field workers met with brothel managers about condom use; the midwife or nurse provided condoms and medications and was the main person responsible for risk reduction counseling on prevention of sexually transmitted infections (STIs), STI treatment, and condom use; and anal sex and sometimes oral sex were also discussed. Social workers were the official study “counselors” in terms of social problems, whereas doctors dealt with counseling on clinical problems, especially HIV pre- and post-test counseling. Often people came to the social worker after their doctor visit to ask more questions about treatment or just to talk about problems at home, illness, children, or partners in a relaxed atmosphere without time limits.
(Population Council and MIRA), while others relied on individual sites to develop site-specific SOPs for risk reduction counseling.

Protocols and sites also took different approaches to the type of staff used to address specific counseling topics—such as risk reduction strategies, family planning, HIV/STI prevention and care, and adherence to the study product. While designated counselors provided much of the counseling that occurred, other staff (including study doctors, social scientists, nurses and clinicians, social workers, pharmacists, field and outreach workers, and peer educators) also received training on how to counsel on specific topics. At some sites, only study nurses or doctors provided counseling on more clinical matters, such as STI prevention and treatment or contraception. Variations also existed in how counselors were trained, the content and frequency of refresher trainings, and the mechanisms used for supervising and supporting counseling staff.

Despite concerns voiced by advocates in the past, including GCM, we saw no evidence that study staff ever compromised risk reduction services in order to “facilitate” the research. In response to concerns over potential conflicts of interest, some stakeholders in the HIV prevention research field have recommended that entities outside of the research enterprise conduct risk reduction counseling rather than staff employed by the study. Both the UNAIDS ethics guidelines for biomedical prevention trials and the South African MRC suggest that such a strategy could address perceived or real conflicts of interest between an investigator’s obligation to minimize participant risk of HIV infection and the need for infections to occur in order to evaluate a product’s effectiveness in preventing HIV.43,44 We found no evidence to support this potential concern. In fact, we observed the opposite—that counselors across sites were so careful to emphasize the unknown effectiveness of the experimental product, the message given to participants may have overemphasized condoms to the point that women who could not negotiate condom use were advised, or understood, that they should not use the gel alone (see Section 5.2.1). Also, 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.

Furthermore, some staff and investigators that we interviewed argued strongly against bringing in an outside group to conduct risk reduction counseling. They noted that under ethics rules, the ultimate responsibility for the quality of participant counseling lies with investigators. Outsourcing counseling would inappropriately relieve investigators of this critical ethical obligation. Moreover, it would be impossible to guarantee the quality of risk reduction counseling if it were outsourced and no study staff were involved. Outsourcing would also introduce more staff into the picture, potentially making relationships even more confusing for participants. Finally, if study sites used research dollars to contract with outside entities, they too would financially benefit from the research, potentially undermining their perceived independence.

5.1.2 Promotion and Provision of Condoms

Condoms are the best-known way to prevent sexual transmission of HIV, and all sites promoted and provided male condoms at each study visit, usually with no limit on the number of condoms women could receive. While all sites reported providing instructions on proper condom use using a penile model, only four out of nine sites actively taught condom negotiation skills (see Table 2). At the Population Council’s Gugulethu site, staff members reported that condom use among participants had increased significantly over time, especially among younger and unmarried women; nonetheless, some women reported that their partners “chose gel over condoms.” Others noted that women reported an enhanced ability to negotiate condom use while in the study. Their male partners saw condom use as a trial-related obligation, but after the trial ended, their
partners were no longer willing to use condoms. At several sites, staff expressed concern that the risk of study participants might return to pre-trial levels after the study closed, particularly in areas where access to condoms was limited and/or costly (see Case Study 1, Provision of Condoms in Cotonou, Benin).

In principle, female condoms were available at most study sites, with the exception of three: the MIRA study, where the protocol discouraged the use of female condoms with a diaphragm, and at sites in Nigeria (FHI CS and FHI SAVVY®), where female condoms were not available in-country at the time the FHI studies were conducted. However, even at sites where female condoms were available, staff typically provided them only if participants requested them, and did not integrate female condoms into overall risk reduction counseling. Most study staff interviewed assumed that female condoms were too expensive or inaccessible, or that there was no consumer demand and therefore they were not worth promoting as part of risk reduction efforts. Across sites, female condom uptake was very low, and the presence and knowledge of female condoms was limited in the surrounding communities at-large. Study counselors and clinicians did not demonstrate female condom use or teach insertion, except at the MDP Mwanza site, where counselors performed female condom demonstrations with the use of a penile model. Although anecdotal evidence suggests that some men initiate female condom use in this way, such demonstrations do not empower women to use the female condom or clearly demonstrate self-insertion.

### Table 2. Condom Provision, Demonstration, and Skills

<table>
<thead>
<tr>
<th>Site</th>
<th>Male condoms provided</th>
<th>Male condom demonstration(s)</th>
<th>Condom negotiation skills taught</th>
<th>Female condoms provided</th>
<th>Female condom demonstration(s)</th>
</tr>
</thead>
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<td>Harare, Zimbabwe</td>
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<td>✓</td>
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<td>(using penile model)</td>
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<td>Mwanza, Tanzania</td>
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</tr>
<tr>
<td>Nigeria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site not visited</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FHI SAVVY</strong></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nigeria and Ghana</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site not visited</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Since our site visit, the MDP site in Unkhanyakude District, South Africa, has made female condoms available in the study clinics, and all counselors have vaginal models with which to demonstrate insertion and use.
Studies show that the female condom is equally effective in reducing STI transmission as is the male condom, and experts consider it equally effective, if not more effective, against HIV. Use of the female condom is expanding worldwide, subsidized supplies are increasingly available, and newer, easier to use, and less costly models are becoming available. Given this, there is no reason not to promote and provide female condoms to the same degree as male condoms; and in fact, increasing knowledge and awareness would be a tool for increasing demand among women and their partners and could lead to an increase in the number of condom-protected sex acts overall.

**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.

### 5.2 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.

Across sites, we observed significant inconsistencies in the messages given to participants regarding gel use, especially around what should happen when condom use is not possible. We as a field must pay increased attention to developing clear, consistent messages on product adherence and to training staff on how to deliver these messages.

Likewise, the contextual realities of many of the communities where trials are taking place pose challenges for meeting the psychosocial needs of participants through referrals. Given this, sites should better equip staff to deal with the various issues participants bring to counseling sessions, including but not limited to domestic violence.

Other observations included the need to separate the collection of sexual behavior data (i.e., study product adherence data) from risk reduction counseling, and the urgent need for increased psychosocial support for study staff, in particular, study counselors.

#### 5.2.1 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 also encouraged women, if possible, to disclose gel use to their partners (Population Council, MIRA, MDP, and HPTN 035).

Most studies combined counseling on gel use with counseling on condom use by employing a hierarchical message (MDP Africa Centre, CONRAD Benin, MIRA, FHI CS, FHI SAVVY®). 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.

Other studies provided separate counseling on gel adherence, and emphasized more strongly the role that consistent gel use plays in the successful completion of the study. At the MDP Mwanza site, for example, counselors work with clients on risk reduction, while clinicians or gel coordinators counsel specifically on gel use and gel adherence. Some sites supplemented hierarchical messages with explicit messages about gel adherence. At HPTN 035 sites, for example, counselors were instructed to state, “In order to properly test if the gel protects against HIV, it is important that you use your gel in every sex act, even when condoms are not possible.” (See Case Study 2.)

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 (see Table 3). We also found substantial confusion over what message counselors were to give if women were unable to use condoms. Some investigators at the
## Table 3. Messages Around Condom and Gel Use

<table>
<thead>
<tr>
<th>Site</th>
<th>Counseling message per protocol and desk review</th>
<th>Counseling message per site visit and anecdotal evidence</th>
<th>Messages consistent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPTN 035</strong></td>
<td>Consistent use of condoms is the only known way to prevent sexual transmission of HIV. It is important that you use your gel in every sex act even when condoms are not possible.</td>
<td>Use gel at all times (even if condoms are not used); i.e., it is important that you use your gel during every sex act, even when condom use is not possible.</td>
<td>Yes</td>
</tr>
<tr>
<td>Harare, Zimbabwe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population Council Gugulethu, South Africa</td>
<td>Condoms are the best-known way to protect yourself from getting HIV/AIDS and most other STIs during sex. You and your sexual partner should use condoms every time you have sex because [the gel] has not yet been shown to prevent HIV, and you may be using the comparator gel, which has not been shown to prevent HIV.</td>
<td>The ideal is to use the gel and condoms every time. If you cannot use condoms, use the gel and know that you are not protected.</td>
<td>No</td>
</tr>
<tr>
<td>Population Council Soshangwe, South Africa</td>
<td>Condoms are the best-known way to protect yourself from getting HIV/AIDS and most other STIs during sex. You and your sexual partner should use condoms every time you have sex because [the gel] has not yet been shown to prevent HIV, and you may be using the comparator gel, which has not been shown to prevent HIV.</td>
<td>Use condoms and gel every time you have sex. “(Counselors) do not say use gel even if you can’t use a condom for fear that women would stop using condoms.” “Other study staff reported that “participants are told that it is important to always use condoms but that if they cannot use a condom, that they must use the gel anyway.”</td>
<td>No</td>
</tr>
<tr>
<td>MDP 301 Unkhanyakude District, South Africa</td>
<td>Participants are asked to use the gel during all episodes of sexual intercourse during the study, and because it is not known if the gel prevents HIV transmission, it is best that condoms are used with gel whenever possible.</td>
<td>“We want you to use condoms and the gel together every time; if you can’t use gel and condoms, use condoms; even if you can’t use condoms, still use gel.” Others reported that women are told to always use gel and condoms and do not deviate from that message.</td>
<td>No</td>
</tr>
<tr>
<td>MDP 301 Mwanza, Tanzania</td>
<td>Participants are asked to use the gel during all episodes of sexual intercourse during the study, and because it is not known if the gel prevents HIV transmission, it is best that condoms are used with gel whenever possible.</td>
<td>Clinic staff reported that participants are told to always use gel and condoms together.</td>
<td>No</td>
</tr>
<tr>
<td>CONRAD Cotonou, Benin</td>
<td>Condoms should be used for all sexual contacts with all partners, including sexual contacts with a steady partner.</td>
<td>“Condoms and gel together is obligatory since gel is experimental. What women do after— if they cannot or do not use [condoms]— is their decision.” “Use condoms and gel at every act; if you can’t use condoms, at least use gel.” Attempt to explore obstacles to condom use with participant.</td>
<td>No</td>
</tr>
<tr>
<td>MIRA Harare, Zimbabwe</td>
<td>Hierarchical counseling Script used</td>
<td>Hierarchical counseling (Use all study products. If you can’t use all, use gel and condoms; if you can’t use …)</td>
<td>Yes</td>
</tr>
<tr>
<td>FHI Cellulose Sulfate Nigeria Site not visited</td>
<td>“Always use condoms during sex, together with the study gel. Even if you don’t use a condom, be sure to use the study gel.”</td>
<td>Site not visited</td>
<td>Yes</td>
</tr>
<tr>
<td>FHI SAVVY® Nigeria and Ghana Site not visited</td>
<td>We do not know which study product was assigned to you. We do not know if [the study] gel works at preventing HIV infection. That is why we are doing this research study. It is very important that you try to use a condom with your gel each time you have sex. Your best protection against HIV is not having sex (abstinence). You can decrease your chance of getting HIV by having your sex partners use condoms…. … if you are unable to use a condom, be sure to use your gel.</td>
<td>Site not visited</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

* Per interview with country-level investigator.
Population Council, for example, expressed the belief that encouraging gel use without condoms, even in instances where condom use is not possible, would be unethical. 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. A study counselor at one of the sites we visited told us, “[We] do not say use gel even if you can’t use a condom [for] fear that women would stop using condoms.”

Although not strictly a “standards of care” issue, low adherence to gel use can severely undermine the power of a study to determine a product’s effect. As such, the field has become increasingly aware of the importance of this issue. Significant progress in this regard has recently been made with the convening of a workshop on “Adherence and Its Measurement in Clinical Trials” by the Alliance for Microbicide Development and FHI. A key finding of which was that “Low adherence levels are frequently due, at least in part, to misunderstanding among site staff of key messages conveyed to study participants during adherence counseling.”

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. For instance, in one study, a US-based IRB required investigators to add a line to the informed consent document stating that, “the only way to prevent HIV/STIs is not to have sex”—this in a study where being sexually active was an eligibility requirement. In another study, USAID, the study sponsor, requested that the study inform participants of the “medically accurate” failure rate of condoms. Investigators were not willing to talk about condoms in terms of failure rates but instead amended their language to note that “condoms are effective when used accurately and consistently.”

**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.

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1 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.
5.2.3 Counseling on Psychosocial Issues

The extent to which microbicide trials addressed psychosocial issues also varied (see Box 8). 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. For example, the FHI protocols for CS and SAAVY, addressed the issues only insofar as to say that they did not anticipate social harms to be an issue for their participant population.

Part of the variation in how sites responded to the psychosocial needs of participants derived from the availability of community resources for psychosocial support. Some areas had established CBOs and support groups, although most were under-resourced. Other areas, such as Umkhanyakude District of KwaZulu Natal, South Africa, had few if any local resources and had to develop their own strategies for dealing with psychosocial problems when they arose. 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.

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

**Approaches to Psychosocial Needs of Participants and Staff**

- At the HIV Prevention Trials Network (HPTN) 035 site in Zimbabwe, a program psychotherapist came once a month to meet with staff.
- At the Population Council’s Gugulethu site, psychosocial problems such as rape and partner violence were common. Urgent referrals were made to the nearby nongovernmental organization (NGO) Lifeline, but otherwise, problems were handled by study staff.
- At the Population Council’s Gugulethu site, there was a study psychologist on staff who came to the clinic twice a month to mentor and support counselors. The Population Council’s Setshaba site also had a psychologist on staff to address the social problems of participants, provide additional post-test counseling for HIV-positive women, and provide support for staff.
- The Population Council’s Setshaba site is the only site visited that had set up its own support group for women with HIV, using study funds.
- At the Microbicides Development Programme (MDP) Africa Centre site in KwaZulu Natal, staff estimated that approximately one in ten women need help with psychosocial problems. Any mention of a social harm triggered an interview with a social scientist, followed up later by a telephone call. If study counselors felt they could not address the psychosocial issues of a participant, the participant could also see the study psychologist and/or be referred to the Department of Social Welfare or possibly a local NGO.
- In Benin, at the Contraceptive Research and Development (CONRAD) Cellulose Sulfate site, participants and non-participants had access to counseling through all study staff. A fulltime social worker was also available to counsel women on a range of issues.
- The MDP Mwanza site referred participants with psychosocial needs to local nongovernmental and community-based organizations, most of which are faith-based. It is not clear how well the needs of high-risk women are met in these settings.
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.”49 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.”50 “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.”51 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:** 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 staff’s HIV status in the same manner they protect trial participants.

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**Public Availability of Screening and Care for Sexually Transmitted Infections**

- Syndromic management (including treatment) for sexually transmitted infections (STIs) is free, integrated into primary health centers, and available in public health clinics in South Africa (although waits may be long). In Cotonou, Benin, STI screening and care is free only at the central STI clinic.
- STI care is free in Tanzania, although care in the public sector often involves long waits and frequent stockouts of drugs.
- In Harare, Zimbabwe, STI care for women using syndromic management is now integrated into other reproductive health services but is not free of charge.

**Approaches to Screening and Care for Sexually Transmitted Infections and Reproductive Tract Infections Taken by Microbicide Studies**

- Investigators involved in the Family Health International SAVVY® trial were not able to provide frequent diagnosis and treatment for STIs and reproductive tract infections for SAVVY® trial participants because participants reported to neighborhood “outreach centers” for counseling and resupply of study products rather than to clinics. The international principal investigator noted that for subsequent trials, he would recommend a clinic-based design to improve access to care for participants.
5.3 Sexually Transmitted Infection Screening and Care

STIs are proven cofactors that facilitate HIV transmission. 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. Likewise, ethics guidance obliges researchers to ensure access to health care services needed for the safe conduct of trials. 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 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.

5.3.1 Approaches to Testing and Treatment for Sexually Transmitted Infections

In all but one of the studies reviewed—the exception being MDP 301—women who volunteered to be screened for each study received laboratory screening and treatment for STIs, regardless of whether or not they enrolled in the study. Trials provided additional STI and reproductive tract infection services at regular intervals for those women who did enroll as study participants.

All sites regularly tested for some STIs (gonorrhea, chlamydia, and syphilis); some also screened and treated vaginal infections (trichomonas, bacterial vaginosis, and candida). The frequency of testing varied from monthly (CONRAD Benin and FHI CS Lagos) to quarterly (most sites) to annually (HPTN 035 Zimbabwe), with additional testing at screening and enrollment and at the trial’s closure. Treatment was free of charge, and effective drugs were readily available (i.e., study sites did not experience the stockouts common in public STI clinics). Because of the increased risk of urinary tract infections (UTIs) among women using diaphragms, the MIRA study also regularly tested for and treated UTIs.

Overall, the level of STI care that trial participants received in the research setting far exceeded that available in the communities where the trials were taking place (see Box 9). 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. 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.

For example, the frequent use of highly accurate, nucleic acid-based laboratory testing (NAAA) is necessary if researchers want to reliably identify new cases of STIs as part of a research protocol. The main benefit of such tests is that they can identify asymptomatic as well as symptomatic infections (which allows the researcher to compare the incidence of STIs among those using the microbicide versus those using a placebo). But such tests...
are not currently feasible for routine STI services in a community. NAAA requires complex laboratory equipment that must be imported and maintained, as well as highly trained personnel, making it far too costly for resource-poor countries except at the level of a national referral laboratory. The development of low-cost, highly sensitive diagnostic tests for STIs that providers can use at the point of care remains an urgent, unmet need that is beyond the scope of this report or the responsibility of microbicide researchers.

At government health centers, where most women in trial communities seek care, if STI care is available at all, providers use syndromic management. This approach identifies and treats symptoms that correspond to a specific syndrome, for example, “vaginal discharge syndrome,” that can be caused by one or more infectious agents. Providers treat for all infections that can cause those symptoms. A woman without any symptoms would not be identified for treatment, unless she has been referred because a partner has a known STI.

Syndromic management is the national policy in all countries that we visited. WHO recommends syndromic management as an appropriate, effective strategy for STI control in low-resource settings where providers receive adequate training and support, and effective drugs are reliably available. In fact, syndromic management is frequently used in developed country settings because laboratory testing takes time and a woman who is potentially infected with gonorrhea or chlamydia could suffer severe consequences (pelvic inflammatory disease and its sequelae, infertility, tubal pregnancy, etc.) if treatment were delayed until laboratory results were available. In many cases, developed world providers use NAAA to confirm the presence of one or more infections that they have already treated based on their symptoms. Confirmatory laboratory testing may also help avoid the social consequences of telling women they have an STI when in fact they do not.

Although people are frequently infected simultaneously with multiple STIs, syndrome management can result in over-treatment, especially for the syndrome “vaginal discharge,” where providers might treat for gonorrhea, chlamydia, bacterial vaginosis, and trichomonas. Over-treatment increases both the cost and potential side effects of medications. Providers can reduce the risk of over-treatment by adding a speculum exam and simple microscopy to syndromic management. A speculum exam (done in trials to look for lesions related to product) allows the provider to see the cervix and to take a sample of cervical or vaginal discharge to examine under the microscope while the woman waits. Speculum exams are simple, and with microscopy, can identify bacterial vaginosis, trichomonas, candida, and excessive white blood cells that point to a need for treatment for gonorrhea and chlamydia.

Another important STI treatment issue in microbicide trials is whether to provide women with single-dose STI treatment (one pill) that eliminates the need to take doxycycline twice daily or tetracycline four times daily for seven days (common antibiotic treatments for chlamydia). These medications frequently cause gastrointestinal side effects that can lead women to discontinue treatment before they are cured. Many public health systems still rely on doxycycline or tetracycline because single-dose treatment with azithromycin was prohibitively expensive at the time that many national governments adopted their STI guidelines. But prices have now decreased dramatically, and the benefits of using a single-dose treatment that ensures a cure are compelling. While researchers need to support national STI guidelines, they can and should advocate for change when appropriate; in this case, support of procurement of cheap supplies of azithromycin, a simpler, more effective treatment with fewer side effects.

Sites used different STI treatment protocols according to investigator preference and national guidelines (see Table 4). MIRA did not treat possible gonorrhea or chlamydia infections based on symptoms but waited for laboratory diagnosis, which took 1–2 weeks. If a test came back positive, the study traced the participant, and provided treatment. The MDP Mwanza site treats according to local guidelines (which do not provide for single-dose treatment), while the MDP site in KwaZulu Natal, South Africa, follows South African guidelines, which do mandate single-dose treatment. The CONRAD Cotonou site departed from local guidelines to treat chlamydia among study participants with single-dose azithromycin instead of doxycycline for seven days. The MIRA site in Harare likewise departed from national STI guidelines for
Table 4: Sexually Transmitted Infection Prevention, Diagnosis, and Treatment

<table>
<thead>
<tr>
<th>Site</th>
<th>At initial screening</th>
<th>At enrollment</th>
<th>Follow-up</th>
<th>Treatment</th>
<th>Partner treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPIN 035 Harare, Zimbabwe</td>
<td>Screening Visit 1: NG/CT, with NAAA; RPR; STI treatment; risk reduction counseling; condoms</td>
<td>Screening for NG/CT, with NAAA; RPR; STI treatment; risk reduction counseling; condoms</td>
<td>Full STI screening annually and BV, TV screen quarterly and when clinically indicated; UTI test and treatment as needed</td>
<td>Per WHO guidelines; acyclovir for HSV-2</td>
<td>Free diagnosis and treatment for partners of screened-out and enrolled women</td>
</tr>
<tr>
<td>Population Council Soshangwe and Gugulethu, South Africa</td>
<td>Screening for NG/CT, with NAAA; RPR; STI treatment; risk reduction counseling; condoms; wet mount/KOH if indicated</td>
<td>NG; CT; TV; syphilis; wet mount/KOH if indicated</td>
<td>NG; CT; TV; syphilis; wet mount/KOH if indicated at months 9,3,6,12,18,24</td>
<td>Single-dose treatment whenever possible; acyclovir for HSV-2 symptoms</td>
<td>Free treatment; may give treatment dose (erythromycin) for partners (Soshangwe only)</td>
</tr>
<tr>
<td>MDP 301 Unkhanyakude District, South Africa</td>
<td>No STI testing</td>
<td>NG/CT by NAAA; RPR; HSV-2</td>
<td>NG/CT at month 6; HSV-2 at months 9,12; RPR at months 6,12</td>
<td>According to local guidelines; no single-dose treatment; acyclovir only in severe cases</td>
<td>Free diagnosis and treatment; may give treatment dose for partners</td>
</tr>
<tr>
<td>MDP 301 Mwanza, Tanzania</td>
<td>No STI testing</td>
<td>NG/CT by NAAA; RPR; TV</td>
<td>At months 6,12</td>
<td>According to local guidelines; no single-dose treatment or acyclovir</td>
<td>Referral letter</td>
</tr>
<tr>
<td>CONRAD Cotonou, Benin</td>
<td>Screening for NG/CT, with NAAA; RPR; pH; gram stain; pelvic; STI treatment; risk reduction counseling; condoms</td>
<td>Screening for NG/CT, with NAAA; RPR; pH; gram stain; pelvic; STI treatment; risk reduction counseling; condoms</td>
<td>All tests quarterly, as needed and requested</td>
<td>Single-dose oral medications where possible</td>
<td>Free treatment or referral</td>
</tr>
<tr>
<td>MIRA Harare, Zimbabwe</td>
<td>Screening for NG/CT, with NAAA; TV; STI treatment; risk reduction counseling; condoms</td>
<td>RPR; HSV-2</td>
<td>Interval syndromic management except cervicitis (only treated upon PCR results)</td>
<td>Based on national guidelines except NG/CT and PID</td>
<td>Free diagnosis and treatment</td>
</tr>
<tr>
<td>FHI Cellulose Sulfate Nigeria Site not visited</td>
<td>Screening for NG/CT, with NAAA; STI treatment; risk reduction counseling; condoms</td>
<td>Pelvic; wet mount; RPR</td>
<td>Self-vaginal swabs monthly at outreach sites</td>
<td>Based on national guidelines; no acyclovir</td>
<td>Women given partner treatment if requested</td>
</tr>
<tr>
<td>FHI SAVVY® Ghana Site not visited</td>
<td>Screening for NG/CT, with NAAA; RPR; STI treatment; risk reduction counseling; condoms</td>
<td>Pelvic; wet mount; RPR</td>
<td>At month 6</td>
<td>Treatment based on local guidelines</td>
<td>Referral for treatment</td>
</tr>
</tbody>
</table>

BV, bacterial vaginosis; CT, chlamydia; HSV, herpes simplex virus; KOH, potassium hydroxide, widely used in wet mount preparations; NAAA, nucleic acid-based laboratory testing; NG, gonorrhea; PCR, polymerase chain reaction, used to test for sexually transmitted infections; PID, pelvic inflammatory disease; RPR, rapid plasma regain, a screening test for syphilis; TV, trichomonas; UTI, urinary tract infection.

Beyond treating STIs among trial participants, researchers can also advocate for and support improved management of STIs for women, including integrating high quality STI services into antenatal and family planning services (already happening at government clinics in South Africa and Zimbabwe). Quality...
improvements also include tailoring some STI services to the special needs of women with multiple partners, the primary populations enrolled by the Benin and Tanzania sites visited.

**CONSSENSUS RECOMMENDATION:** Laboratory screening and treatment for sexually transmitted infections, 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 sexually transmitted infection (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 sexually transmitted infection (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.

### 5.4 Cervical Screening and Care

As noted already, 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. 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; however, 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, researchers struggle with 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.

Trial sites located in areas where cervical screening, diagnosis, and treatment were available through the national health system provided such care as part of the study. Sites where these services were not available found it difficult to justify cervical screening (see Box 10). The MDP protocol, for example, states that Pap smears will only be provided where local treatment for cervical dysplasia is available (MDP South Africa sites), and the HPTN 035 protocol allows for sites that can provide services to do so (which at the time of writing included all but one site). In Benin and Tanzania, where the public sector does not provide cervical treatment, the trials did not offer routine screening.

At the HPTN 035 site in Zimbabwe, women go through two separate screening visits. In the first, clinicians test them for HIV and some STIs. At the second, they perform a speculum and pelvic exam and Pap smear. This avoids identifying HIV-positive women at screening who also have an abnormal cervical lesion that needs treatment. The Population Council and MDP South Africa sites did cervical screening at the initial screening visit; if women were not eligible for the study and had an abnormal result, they were referred directly into the public system.

Although they are new and overburdened, the South African Government provides complete cervical cancer control services. Screening and
referral by studies probably afforded women earlier entry into the government system than they might otherwise have had. Women already enrolled in studies and found to have abnormalities were fast-tracked through the government service to avoid keeping them “off product” for an inordinate amount of time.

Despite variations in the provision of cervical screening (see Table 5), all sites that performed Pap smears referred women with abnormal smears or suspicious lesions for diagnosis and treatment. The extent to which study sites covered or assisted with the cost of this treatment varied.

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

**Approaches to Cervical Screening**

- In South Africa, there is now free cervical screening on a national level. Public clinics in the research communities we visited conducted Pap smears, although according to the study coordinator in Unkhanyakude District of KwaZulu Natal, most women screened for the study had never had one. South African sites (Microbicides Development Programme [MDP] Africa Centre and Population Council) provided cervical screening at enrollment and at 12-month intervals. At the MDP Africa Centre site, the local ethics committee required the study to perform Pap smears if they were going to do speculum exams. High-grade lesions (which can progress more quickly to cancer) were referred for further care and “fast-tracked” to the gynecology department of a referral hospital. The study subsidized the costs of treatment and transport, if needed.

- At the Population Council’s Setshaba and Gugulethu sites, if a woman’s Pap smear was abnormal at screening but she was otherwise eligible to participate in the study, the study referred her for diagnosis and treatment before she could enroll. At the Setshaba site, high-grade lesions in enrolled women were fast-tracked to Pretoria Academic Hospital and transport to the hospital was provided.

- In Harare, Pap smears are available in local clinics in principle, but services are limited and not free; Zimbabwe is now implementing visual inspection with acetic acid wash. The principal investigator at the HIV Prevention Trials Network (HPTN) 035 site was involved in limited provision of free services to the community through the university teaching hospital, and a study colposcope for the diagnosis of abnormal lesions was available at one of the study clinics. The HPTN 035 site in Harare provided cervical screening at the second screening visit, a participant’s last quarterly visit, and additionally when clinically indicated or per local guidelines. The Methods for Improving Reproductive Health in Africa (MIRA) site in Harare provided Pap smears to participants at enrollment and would repeat Paps if initial results were abnormal.

- The MDP Mwanza site did not provide cervical screening, as no national services were available at the time of our visit. Lesions discovered on speculum exam were referred to the local hospital for biopsy. In one case, the study paid for a participant’s hysterectomy when advanced disease was discovered.

- Contraceptive Research and Development (CONRAD) Benin provided no screening, as no national program exists. Suspicious lesions were referred to a gynecologist, but women had to pay for care unless there was a possibility that the abnormality was related to use of the study product.

- Family Health International SAVVY® Nigeria sent about ten women with suspicious lesions seen on speculum exam for Pap smears. The study paid for the smears.
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

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**TABLE 5. Cervical Screening and Treatment**

<table>
<thead>
<tr>
<th>Site</th>
<th>Pap provided</th>
<th>Diagnosis and treatment of lesions and referral services</th>
<th>Services in the community</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTN 035 Harare, Zimbabwe</td>
<td>At second screening and last quarterly (or as clinically indicated)</td>
<td>Eligible and participating women receive free diagnosis and treatment* by study medical officer or are referred for treatment as appropriate.</td>
<td>Limited local services through university/private sector; VIA being initiated.</td>
</tr>
<tr>
<td>Population Council Gugulethu, South Africa</td>
<td>At enrollment and at 12-month intervals</td>
<td>Referral for diagnosis and treatment* by study gynecologist, or referral (study pays for first referral visit) for eligible women and six monthly follow-up Paps; transport for colposcopy if needed. HIV-positive screened-out women referred with copy of their Pap to facilitate faster service; screened-out women with abnormal Pap who do not return for their results tracked by study.</td>
<td>Complete free services in South Africa, but awareness is low and services are overburdened.</td>
</tr>
<tr>
<td>Population Council Soshanguve, South Africa</td>
<td>At enrollment and at 12-month intervals</td>
<td>Referral for diagnosis and treatment* (study pays for first referral visit); transport provided only for HIV-negative women referred to Pretoria Academic Hospital. Follow-up Pap every six months by study for enrolled women. HIV-positive screened-out women with abnormal Paps who do not return for their results tracked by study.</td>
<td>Complete free services in South Africa, but awareness is low and services are overburdened.</td>
</tr>
<tr>
<td>MDP 301 Unkhanyakude District, South Africa</td>
<td>At enrollment and at 12-month intervals</td>
<td>Participants receive diagnosis and treatment* free at local gynecology hospital; transport sometimes provided.</td>
<td>Complete free services in South Africa, but awareness is low and services are overburdened.</td>
</tr>
<tr>
<td>MDP 301 Mwanza, Tanzania</td>
<td>No</td>
<td>Referral to public services for suspicious lesions.</td>
<td>Very limited private services; no national/local cervical care program.</td>
</tr>
<tr>
<td>CONRAD Cotonou, Benin</td>
<td>No</td>
<td>Referred for suspicious lesions to gynecology hospital at participant expense unless suspected to be study-related.</td>
<td>Very limited private services; no national/local cervical care program.</td>
</tr>
<tr>
<td>MIRA Harare, Zimbabwe</td>
<td>At enrollment (follow-up if any problems)</td>
<td>Referred for diagnosis and treatment* to local clinics (study assisted in finding funding if local services would not cover cost of diagnosis and treatment). Diagnosis and treatment* conducted and paid for by the study for women enrolled in HPV/BV sub-study.</td>
<td>Limited local services through university/private sector; VIA being initiated.</td>
</tr>
<tr>
<td>FHI Cellulose Sulfate Nigeria Site not visited</td>
<td>No</td>
<td>Referred for suspicious lesions to public or private facility at participant expense unless suspected to be study-related.</td>
<td>Limited, private.</td>
</tr>
<tr>
<td>FHI SAVVY Nigeria and Ghana Site not visited</td>
<td>No; some women referred for Pap, cost covered by study</td>
<td>Study was not presented with need to cover treatment; investigators were unsure whether study would have covered cost.</td>
<td>Limited, private.</td>
</tr>
</tbody>
</table>

BV, bacterial vaginosis; HPV, herpes simplex virus; VIA, visual inspection of the cervix with acetic acid wash.

* Diagnosis and treatment include colposcopy, taking biopsy for histology examination, treatment with cryotherapy or loop electrosurgical excision procedure (LEEP) according to results, and/or follow-up with more frequent Paps or colposcopy. Cervical cancers are referred to public hospitals for care.
access to services by offering training to public-sector providers in screening colposcopy, including appropriate low-tech approaches such as visual inspection of the cervix with acetic acid wash (VIA) where they are approved.

5.5 Pregnancy and Contraception

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.55 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.56,57

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.

GCM has argued that onsite access to contraception is a reasonable and prudent benefit to provide participants in HIV prevention trials. This is a viable, low-cost opportunity to benefit women’s health and contributes to optimal study outcomes. While researchers have made recent attempts to address the issues of pregnancy in trials, some put many of these strategies in place mid-way through the studies, when high pregnancy rates were identified, and sometimes without properly training staff. For future trials, more proactive thought and planning need to go into addressing the needs of pregnancy management, provision of contraception, and counseling of women who become pregnant in the course of HIV prevention trials.

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 package58 and that pregnancy should not fundamentally exclude women from participation in research trials.59

5.5.1 Contraception

Trials used different strategies to address women’s contraceptive needs across sites (see Box 11). Some sites referred women to local facilities for all contraceptive services; some counseled women and then referred them for provision of contraception; and some provided both counseling and contraceptives onsite. Those providing contraceptives onsite usually provided options consistent with the local method mix—the most common methods being Depo-Provera, an injectable contraceptive, and oral contraceptive pills.

As noted, many sites added contraceptive services during the course of trials when the number of unplanned pregnancies began to threaten the scientific integrity of the trial. New strategies developed to limit pregnancies included:

1. Adding family planning counseling and/or provision of methods (per protocol) mid-way through trials (Population Council, CONRAD, and FHI).
2. Asking enrolled women if their minds had changed and they now desire pregnancy. If yes, the women were discontinued from the trial (FHI CS Lagos).
3. Intensifying counseling efforts for women not using effective methods of contraception (MDP Umkhanyakude District, South Africa).

Sites that anticipated the problem of high pregnancy rates and provided family planning methods early on had the lowest pregnancy rates. But variations in pregnancy rates also reflected the underlying acceptability of contraceptive use among the study populations and the communities at large.
prevalence rates (the percentage of women between 15 and 49 years who are practicing any form of contraception) among women in the east and southern African regions averaged around 50 percent. In West Africa, national contraceptive prevalence rates ranged from 19 percent in Benin to 13 percent in Nigeria and 25 percent in Ghana (see Table 6). The West African sites also enrolled women with multiple sex partners who according to research staff preferred condoms for contraception and disease protection, which could account in part for the low contraceptive uptake.

Many of the investigators and staff interviewed expressed their preference that participants use more reliable long-acting methods of contraception in addition to condoms (also used for HIV/STI risk reduction). At several sites, providers expressed a clear bias toward injectable contraceptives over other, user-controlled options.

Despite universal concerns about pregnancy, disagreement remains on the appropriateness of requiring the use of non-barrier contraceptive methods for study participation. Although women who wish to avoid long-acting contraceptives can choose not to join a study, some argue that it is an infringement of women’s rights to mandate what method they use. None of the sites we visited required the use of a particular form of contraception, but a recent microbicide study of tenofovir gel required the use of some form of long-acting contraception (e.g., hormonal methods such as oral contraceptives or injectables). Women who have undergone tubal ligation were also eligible to participate.

**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 relationships between contraceptive use, informed choice, and other study procedures.

### 5.5.2 Emergency Contraception

The standards of care mapping exercise did not include questions about the use of emergency contraception, and staff did not spontaneously raise the issue during interviews. Emergency contraception is available in all of the countries visited and its provision, paired with proper counseling, could help lower pregnancy rates among participants, as well as contribute to community awareness about this important addition to fertility control. Given to women to keep at home in case of condom failure, or unplanned, unprotected sex, emergency contraception could lower pregnancy rates, thereby increasing study power, and prevent unsafe abortion.

**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.

### Table 6. Provision of Contraception

<table>
<thead>
<tr>
<th>Site</th>
<th>Contraception provided by study</th>
<th>When was contraception provided</th>
<th>Local contraceptive prevalence rates*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTN 035 Harare, Zimbabwe</td>
<td>Depo, OCPs provided (Norplant for fee); prescription or referral for methods not provided through study</td>
<td>Provided at start of trial</td>
<td>54% nationally</td>
</tr>
<tr>
<td>Population Council Gugulethu, South Africa</td>
<td>Most commonly, OCPs and injectables</td>
<td>Provided at start of trial</td>
<td>60% nationally; 60% study population</td>
</tr>
<tr>
<td>Population Council Soshanguve, South Africa</td>
<td>Same methods provided by DoH provided (most commonly, OCPs and injectables)</td>
<td>Provided mid-way through trial per protocol amendment</td>
<td>60% nationally</td>
</tr>
<tr>
<td>MDP 301 Unkhanyakude District, South Africa</td>
<td>Study dispenses DoH supplies: OCPs, injectables, emergency contraception (3-month supply), referral for tubal ligation if desired</td>
<td>Provided at start of trial</td>
<td>60% nationally; 53% study population</td>
</tr>
<tr>
<td>MDP 301 Mwanza, Tanzania</td>
<td>Locally available provided; OCPs and Depo; study obtains supplies from DoH</td>
<td>Provided at start of trial</td>
<td>26% nationally; 41% unmarried women from study population; 26% married women from study population</td>
</tr>
<tr>
<td>CONRAD Cotonou, Benin</td>
<td>Locally available provided</td>
<td>Provided mid-way through trial; injectables since October 2006</td>
<td>19% nationally</td>
</tr>
<tr>
<td>MIRA Harare, Zimbabwe</td>
<td>Provided; referrals for methods not available through the study</td>
<td>Provided at start of trial</td>
<td>54% nationally</td>
</tr>
<tr>
<td>FHI Cellulose Sulfate Nigeria Site not visited</td>
<td>Not provided; counseling, educational materials, and referrals to family planning clinics provided</td>
<td>Not provided; family planning counseling provided at start</td>
<td>13% nationally</td>
</tr>
<tr>
<td>FHI SAVVY® Nigeria and Ghana Site not visited</td>
<td>Not provided; counseling and referrals to family planning clinics provided</td>
<td>Not provided; family planning counseling provided mid-way through trial</td>
<td>13% Nigeria, nationally; 25% Ghana, nationally</td>
</tr>
</tbody>
</table>

Depo, Depo-Provera; OCPs, oral contraceptive pills.

*National contraceptive prevalence rates (CPR) taken from the 2007/2008 Human Development Report; CPR for study populations quoted by study staff during site visits.
5.5.3 Managing Pregnancy

Seven out of the nine sites reviewed provided referrals for antenatal care and limited pregnancy counseling (the exceptions being the FHI CS and FHI SAVVY® Lagos sites; see Table 7 and Box 12). The accessibility and cost of antenatal care in the communities where trials were taking place varied by setting; all services were free in South Africa, whereas in Benin, Nigeria, Tanzania, and Zimbabwe, women were required to pay for services.

If an HIV-positive woman became pregnant (or was identified as being pregnant at screening), she was counseled and referred for prevention of mother-to-child transmission of HIV (PMTCT) services, which at the time of our visits, were available free in all study communities.

Generally, participants who became pregnant were allowed to continue with study visits but were taken off product temporarily. The exceptions were the Population Council Carraguard® study, which discontinued women completely from the study if they became pregnant, and the MIRA trial, which allowed women to continue diaphragm use throughout pregnancy. After our visit, the MDP protocol was amended to allow women who wished to do so to restart gel after the end of their pregnancies if they were still within the follow-up period.

Study staff expressed the difficulty they faced in discontinuing women either from the study or from gel use due to pregnancy. Despite repeated messages that women who become pregnant will no longer be able to use the study

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### TABLE 7. Management and Consequences of Pregnancy for Participants

<table>
<thead>
<tr>
<th>Site</th>
<th>Per protocol</th>
<th>Care and referral</th>
<th>Termination of pregnancy (TOP)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTN 035 Harare, Zimbabwe</td>
<td>Can continue in study off gel; can resume gel use with negative pregnancy test</td>
<td>Referred for antenatal care (nominal fee)</td>
<td>TOP permitted to preserve physical health; save a woman’s life; and in cases of rape, incest, and/or fetal impairment</td>
</tr>
<tr>
<td>Population Council Gugulethu, South Africa</td>
<td>Permanently discontinued from trial</td>
<td>Referred for antenatal care (free)</td>
<td>TOP permitted without restriction; gestational limit of 12 weeks; up to 20 weeks under some circumstances</td>
</tr>
<tr>
<td>Population Council Soshanguve, South Africa</td>
<td>Permanently discontinued from trial</td>
<td>Referred for antenatal care (free)</td>
<td>TOP permitted without restriction; gestational limit of 12 weeks; up to 20 weeks under some circumstances</td>
</tr>
<tr>
<td>MDP 301 Unkhanyakude District, South Africa</td>
<td>Can continue in study off gel; can resume gel use with negative pregnancy test</td>
<td>Referred for antenatal care (free)</td>
<td>TOP permitted without restriction; gestational limit of 12 weeks; up to 20 weeks under some circumstances</td>
</tr>
<tr>
<td>MIRACOLO Mwanza, Tanzania</td>
<td>Can continue in study off gel; can resume gel use with negative pregnancy test</td>
<td>Referred for antenatal care (free unless high-risk)</td>
<td>TOP prohibited; explicit exception to save a woman’s life</td>
</tr>
<tr>
<td>CONRAD Cotonou, Benin</td>
<td>Can continue in study off gel; can resume gel use with negative pregnancy test</td>
<td>Referred to gynecologist (fee for service)</td>
<td>TOP prohibited except to preserve physical health; save a woman’s life; and in cases of rape, incest, and/or fetal impairment</td>
</tr>
<tr>
<td>MIRA Harare, Zimbabwe</td>
<td>Can continue in study; pregnant participants are not required to discontinue diaphragm use but may choose to</td>
<td>Referred for family planning services are provided (nominal fees)</td>
<td>TOP permitted to preserve physical health; save a woman’s life; and in cases of rape, incest, and/or fetal impairment</td>
</tr>
<tr>
<td>FHI Cellulose Sulfate Nigeria Site not visited</td>
<td>Can continue in study off gel; can resume gel use with negative pregnancy test</td>
<td>No assistance with referral for pregnancy care</td>
<td>TOP prohibited; explicit exception to save a woman’s life</td>
</tr>
<tr>
<td>FHI SAVVY® Nigeria and Ghana Site not visited</td>
<td>Can continue in study off gel; can resume gel use with negative pregnancy test</td>
<td>No assistance with referral for pregnancy care</td>
<td>Nigeria: TOP prohibited; explicit exception to save a woman’s life; Ghana: TOP permitted to preserve mental health; save a woman’s life; and in cases of rape, incest, and/or fetal impairment</td>
</tr>
</tbody>
</table>

*The laws surrounding termination of pregnancy differ among the countries where microbicide trials have taken and are taking place. The extent of the information given by study staff to participants regarding termination of pregnancy, therefore, is influenced by these conditions. Regardless of the legality of termination of pregnancy, the authors of this report argue that participants should be provided information on the dangers of unsafe abortion and on when and where to seek care in case of post-abortion complications.
gel (or continue in the study), many women who became pregnant were surprised to learn that their participation in the study would change. Early termination from the trial was an emotional issue for many women, as well as a financial one, as many women expressed the loss they felt in having to leave the trial.

**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:** 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.

### 5.5.4 Termination of Pregnancy

At every site we visited, participants received little or no information regarding abortion services (where legal), the risks of unsafe abortion, and the local availability of post-abortion care (see Box 13). 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.

Study populations consisting primarily of women with multiple partners in Benin, Nigeria, and Tanzania also had the highest pregnancy rates and no access to legal abortion. In Benin, study staff confided that most women reported terminating their pregnancies illegally. These women often could not afford to continue a pregnancy, as it interfered with their ability to work and generate income. Investigators interviewed working on the Nigeria-based trials, where, like Benin, there is no access to legal abortion services, expressed similar challenges among their study populations. While study staff understood this reality, they did not discuss the dangers of unsafe abortion or where to go for post-abortion care if needed.

Even in South Africa, where abortion is legal, most study staff were uncomfortable talking about it, saying “we are not trained to talk about that.” Some counselors and nurses provided information about local abortion services if participants asked but did not volunteer the information. At the Population Council Gugulethu site, counselors referred pregnant women who expressed an interest

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**Approaches to Pregnancy Testing and Referral**

- Pregnancy counseling and referrals for antenatal care were given at seven of nine sites. Family Health International (FHI) Cellulose Sulfate and FHI SAVVY® Lagos did not refer women to antenatal care services.
- At the Contraceptive Research and Development (CONRAD) site in Benin, pregnant women were referred to a gynecologist for counseling, if needed. Study clinicians reported that they did not counsel on pregnancy.
- Antenatal care is readily accessible and free in South Africa; in Zimbabwe, antenatal care is accessible and low-cost, with women required to pay nominal user fees; in Tanzania, antenatal care and delivery are free, but if the pregnancy is high-risk, a woman must pay; antenatal care and delivery are not free in Benin or Nigeria.
- All studies follow women for pregnancy outcomes.
- All sites were located where prevention of mother-to-child transmission of HIV services were available, and pregnant, HIV-positive women were referred to these programs, which were usually offsite.

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**What Is Values Clarification Training?**

Values clarification training seeks to help providers understand how their values affect their actions and behaviors and how to, in light of their identified values, provide unbiased and nonjudgmental care to patients whose values may differ from their own.
in termination to study nurses for “options counseling,” for which they had not been trained.

While personal beliefs can contribute to the discomfort of discussing termination of pregnancy—highlighting the need for values clarification training—discussions of abortion services are also constrained by real or perceived restrictions from donors and sponsors. In U.S. Government-funded studies (which include all but the MDP sites), there is confusion over the degree to which US policy restricts the ability of counselors to provide information about pregnancy options, abortion services (where legal), dangers of unsafe abortion, and the availability of post-abortion care.

**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.

### 5.6 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 NGOs or 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 TB; and information and services for STIs, sexual health, family planning, and managing pregnancy, including PMTCT.

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

5.6.1 Findings: HIV Care and Treatment

Every trial site that we visited in October and November 2006 had free government HIV/ART services available in the community (see Table 8). These programs tended to be new and, depending on location, overburdened or underutilized. In addition, 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 (see Table 9).

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 (see Table 10). There were some exceptions, however (see Case Study 3). At one site, clinicians offered CD4 counts to women who were found to be HIV-

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

### Table 8. HIV Care and Treatment Available Publicly Around Trial Sites

<table>
<thead>
<tr>
<th>Country*</th>
<th>HIV care and treatment available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benin</td>
<td>In Cotonou, the government provides HIV care and treatment, including free ART. The DIST, one of five sites in the city that dispense ART, served as the main CONRAD study clinic. CONRAD supported services for high-risk women and their partners in collaboration with the national AIDS control program, and provided the bulk of funding before it closed the CS trial prematurely.</td>
</tr>
<tr>
<td>South Africa</td>
<td>HIV care and treatment, including ART, is free for all South Africans, and available in the communities surrounding all of the sites we visited. Services have been very slow to start up, and distribution is unequal. Regular monitoring with CD4 counts (and sometimes viral load) is done, and PMTCT services are available, including triple therapy for eligible mothers. The quality of services and distance to ART services varies. While it is excellent in some places, clinics tend to be overburdened, with long clinic waits and a serious lack of human resources.</td>
</tr>
<tr>
<td>Tanzania</td>
<td>HIV care and treatment are technically free in Tanzania, but patients are often charged unofficial “registration” fees. The national treatment program was just more than a year old at the time of our visit, and people were distrustful of ART. They did not necessarily believe that antiretrovirals worked, as they had yet to see the positive effects of treatment. Access to HIV treatment and care at trial sites like MDP Mwanza can be problematic for study participants because of the distance and cost of transport.</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>HIV care and treatment is provided at very low cost, but the cost of the baseline testing required for eligibility (reported as approximately 100 USD at the time of our visit) is prohibitive for most. Social welfare grants are available for people with HIV but are administratively complex and have to be renewed yearly. A local USAID-funded NGO that provides the HIV counseling for government services provides assistance with grant applications.</td>
</tr>
</tbody>
</table>

* ART, antiretroviral therapy; CONRAD, Contraceptive Research and Development; CS, Cellulose Sulfate; MDP, Microbicides Development Programme; PMTCT, prevention of mother-to-child transmission of HIV.

* As the assessment of the care and treatment available publicly around trial sites was based on information gathered during our site visits, Ghana and Nigeria have been omitted here.
CASE STUDY 3
Care and Treatment for HIV at the Contraceptive Research and Development Site, Cotonou, Benin

The Contraceptive Research and Development (CONRAD) study was implemented within the context of a poorly resourced, fee-for-service public health system with a study population at high risk for HIV. Women were mostly mobile, many from Ghana and Nigeria, had little education, and supported families back home. CONRAD took over a Canadian government-funded intervention, Projet Sida, that had begun more than a decade earlier to provide services to sex workers in Benin, which consisted of monthly checkups, including sexually transmitted infection (STI) syndromic management, HIV voluntary counseling and testing, and behavior change communication provided through a network of peer educators. Field activities were conducted through local nongovernmental organizations and project field workers in brothels, nightclubs, bars, hairdressers, and other work places. Canadian funding ended in June 2006. As the Programme Nationale de Lutte Contre le Sida (PNLS, Benin’s national AIDS control program) began the process of finding funds and taking over these services, the CONRAD study filled the gap by taking over management and funding of the program for all but two staff, continuing to provide clinic and community-based services for all women at high risk and recruiting for the microbicide trial. The Dispensaire Pour les Maladies Sexuellement Transmissibles (DST, the STI reference clinic for the national AIDS control program) was the main study clinic was located on the site of the local community hospital, allowing for easy referral for non-study related problems (for which women paid). A second study clinic, in a suburban area of Cotonou, targeted local women living with their families and working clandestinely; these women were considered at greater risk because of the secretive nature of their night work and their fear of seeking health care because of stigma.

Sex workers and brothel managers who had been trained as community peer educators were vital to maintaining high levels of knowledge of risk reduction and condom and lubricant use among women, bringing women to the clinics regularly for STI management and counseling in risk reduction, providing HIV care for those who were infected, and maintaining study participation. Free lubricants and condoms made available through Projet Sida prior to the microbicide study laid a foundation for gel acceptance and high condom use. However, women exiting the study were concerned about lack of access to study gel and condoms. In response, and in an effort to encourage women to return unused study products, CONRAD provided each study participant with a few tubes of a commercial lubricant at study closure. Women participating in Projet Sida activities were well-aware that repeated sex without condoms and lubrication is less safe, and despite CONRAD’s efforts, feared they would not be able to afford even condoms going forward.

Despite the high-risk population in which this study took place, participants and their peers had equal access to services tailored to meet their special needs. Similarly, the study site offered the same evaluation and care to women who tested positive for HIV at study screening as it did to women who seroconverted during the study. Most women at the Cotonou DST clinic had been seen there regularly before coming for study screening and continued to access services as usual (including HIV care) after testing positive. Familiarity with the study provider and ongoing peer support in their communities (via study peer educators) helped to maintain regular monthly visits.

CONRAD’s goal was to conduct the microbicide trial within the context of these services and fund them for all women as the national government progressively took them over. The early closure of the Cellulose Sulfate study threatened both clinics with closure, but fortunately, a new Canadian research project took over staff and services jointly with the PNLS—-with reduced staff and services, however. The example of the research partnership established by CONRAD in Benin highlights the fragility of the best intentions of programs funded from the outside.

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 (see Box 15 and Table 11). 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 (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.”

But even when care was available to women through a study, screened-out women often did not return voluntarily for additional services. Staff cited many possible 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.

Overall, we found that sites that were co-located or partnered with existing
TABLE 9. SERVICES PROVIDED TO WOMEN WHO SEROCONVERT DURING STUDY PARTICIPATION

<table>
<thead>
<tr>
<th>HIV PREVENTION TRIAL SITE</th>
<th>ONGOING COUNSELING</th>
<th>STUDY-RUN POSITIVE SUPPORT GROUP</th>
<th>FACILITATED REFERRAL TO ART PROGRAMS (PMTCT IF NEEDED)</th>
<th>UPTAKE OF REFERRAL SERVICES TRACKED</th>
<th>OP SCREENING, PROPHYLAXIS, AND/OR OI TREATMENT</th>
<th>CAN REMAIN IN STUDY/ON PRODUCT</th>
<th>TB SCREEN AND/OR CHEST X-RAY</th>
<th>CD4 COUNT, LFT, FBC</th>
<th>WHO STAGING</th>
<th>OPPORTUNITIES</th>
<th>ANTIRETROVIRALS</th>
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<tr>
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<td>✔</td>
<td>✔</td>
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<td>✔</td>
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<td></td>
<td></td>
<td>Referral</td>
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<td>✔</td>
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<td>Referral; can cover cost for duration of study if needed</td>
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</table>

ART, antiretroviral therapy; FBC, full blood count; LFT, liver function test; OI, opportunistic infection; PMTCT, prevention of mother-to-child transmission of HIV; TB, tuberculosis; WHO, World Health Organization.
TABLE 10. Services Offered Through a Study to Seroconverters Versus Screened-Out Women

<table>
<thead>
<tr>
<th>HIV-positive at screening</th>
<th>All sites</th>
<th>Some sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Post-test counseling</td>
<td></td>
<td>• Assistance with referrals (scheduling appointments and/or accompaniment)</td>
</tr>
<tr>
<td>- Minimum of one additional counseling session</td>
<td></td>
<td>• Referral without assistance</td>
</tr>
<tr>
<td>- Referral to HIV antiretroviral therapy (ART) programs with some monitoring of uptake of services</td>
<td></td>
<td>• Referral with letter to social services and nongovernmental organization for waiver of costly laboratory fees</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Referral plus World Health Organization staging, CD4, opportunistic infection (OI) assessment and prophylaxis, and ongoing psychosocial support for duration of study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• OI treatment and ART (Benin)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV seroconverters</th>
<th>All sites</th>
<th>Some sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Ongoing counseling on positive living, disclosure, and how to access care/support</td>
<td></td>
<td>• OI screening, prophylaxis, and/or treatment (four of nine)</td>
</tr>
<tr>
<td>- Referral facilitated to ART programs (prevention of mother-to-child transmission of HIV if needed)</td>
<td></td>
<td>• Tuberculosis screening (four of nine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CD4 count (four of nine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Liver function test, full blood count (three of nine)</td>
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<tr>
<td></td>
<td></td>
<td>• Chest x-ray (three of nine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Positive support group (two of six)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Uptake of referral services tracked (eight of nine)</td>
</tr>
</tbody>
</table>

**Approaches to Care and Support for Seroconverters**

- **Late in trial implementation,** Methods for Improving Reproductive Health in Africa (MIRA) instituted a standard treatment and care package that provided women who seroconverted with psychosocial support and counseling, opportunistic infection (OI) screening, monitoring of HIV disease with CD4 cell counts and other indicators of immune status, and antiretroviral therapy (ART) while the trial was ongoing (but not post-trial). In Zimbabwe, the study site covered the cost of mandatory baseline testing to ensure that patients could access public HIV services by the time they needed services; for most, this likely occurred after study closure.

- **Although seroconverters in the Population Council study were discontinued from participation,** a study-funded support group at the Soshanguve site provided weekly counseling, a soup kitchen, income-generating activities, and medical care for seroconverters and screened-out women. Medical care included six monthly CD4 counts, tuberculosis (TB) screening, OI assessment, and referral to Department of Health (DoH) clinics for care and prophylaxis. Participation was intermittent because of transport costs to the clinic (there were no reimbursements) and women’s competing priorities, especially the need to access treatment at the hospital some distance away.

- **At the Population Council’s Gugulethu site,** women who seroconverted as well as those who tested HIV-positive at screening were referred to one of several nearby DoH-run primary health centers (PHCs) through a memorandum of understanding (MOU) that provided integrated HIV care, including diagnosis and treatment of OIs, TB, and sexually transmitted infections. Antiretrovirals were provided at only one of these clinics. The township of Gugulethu benefits from multiple research projects that involve its PHCs, and HIV/ART services are more advanced than at other South African sites. At the Setshaba site, the same MOU-formalized services exist, but ART is provided at a large hospital approximately 18 km away from the study clinic. This clinic is overburdened, has a substantial waiting list, and transport is difficult for many participants.
government care facilities were generally able to provide the broadest range of HIV services (see Case Study 4). 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).

CONRAD was also the only trial to secure funds before the trial began for women to receive HIV care, including ART, after the close of the trial for five years, whenever they became medically eligible. However, it is yet unclear how this commitment will formally be operationalized across sites. At the Benin site, the national AIDS control program (PNLS) plans to combine the money set aside by CONRAD for the care of seroconverters into a general account constituting a government fund made up of money secured from outside partnerships to provide needed care for all HIV-infected persons when GFATM grants prove inadequate. The national AIDS control program has committed to providing CS seroconverters with the standard care available in Benin but not specifically using the CONRAD funds.

According to the Benin site investigator, authorities at the national AIDS control program are confident they will be able to provide adequate care to the former trial participants who will need it and have more generally made commitments to provide free HIV/AIDS care throughout Benin.

**Consensus Recommendation:** Future trials should pursue concrete steps to improve referral systems and facilitate access to government or nongovernmental organization-run HIV/antiretroviral therapy programs for women who screen HIV-positive at enrollment by providing World Health Organization staging and CD4 counts at the initial screening visit.

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**Case Study 4**

Care and Treatment for HIV at the Microbicides Development Programme Africa Centre Study Site, Unkhanyakude District, KwaZulu Natal, South Africa

The three study clinics that comprised Microbicides Development Programme's (MDP) site in Unkhanyakude District of KwaZulu Natal were situated in porta-cabins immediately next to established Department of Health (DoH) clinics. The porta-cabins were purchased with US President's Emergency Plan for AIDS Relief (PEPFAR) funds by the Africa Centre, which started the local antiretroviral therapy program in 2004 at Hlabisa Hospital. Most MDP staff had worked at one time in the public system and knew it and their colleagues well. There was an (unwritten) understanding that recruitment could take place in DoH clinics and that MDP staff would provide primary care for women who visited their clinics for screening or study visits.

Africa Centre study clinicians (working on microbicides and other trials) spent time in the public clinics as well as in research clinics. Women who seroconverted in the microbicide study were encouraged to remain in the study and on gel, so they would have continued access to personalized counseling and care. They were also encouraged to enroll in one of the DoH clinics, where they would receive HIV-specific care when needed after the study. Women who tested positive for HIV at screening were offered an immediate CD4 count and asked to come back in two weeks for the result—at which time, they could receive additional counseling, be assessed for HIV clinical staging, and be treated for any opportunistic infections. If their CD4 count was <250, they would receive a managed referral for ART. If their CD4 count was <250 and they did not return for their result, they were traced by study staff, who would give them their result and encourage them to seek treatment. Women were encouraged to return to the clinic as often as needed for counseling, although most did not. The co-location and close links between the DoH and study clinics enabled a research-care synergy that resulted in better care for women and better study adherence because women came to the study clinic for visits rather than spending time waiting for primary care in the DoH clinics. This provided a welcome decrease in the burden on DoH providers.
Approaches to Care and Support for Women Who Test HIV-Positive at Screening

- At the Population Council Gugulethu site, two extra counseling sessions were offered, plus clinical staging and a tuberculosis (TB) symptom screen. Women were asked to return after two weeks to receive final Pap and sexually transmitted infection (STI) test results and treatment, if necessary, for curable STIs. If a woman’s Pap smear was abnormal, she was given a referral to government services. Women were also referred for HIV care to government services that provided complete care. However, because of stigma, the desire to seek care anonymously, and the lack of an established relationship between women who screened positive and study staff, screened-out women did not often return to the study clinic.

- At the Population Council’s Soshanguve site, the same services as the Gugulethu site were eventually offered. With the initiation of the positive support group, screened-out women could also access services such as CD4 count, evaluation of opportunistic infections (OIs), TB screening, nutritional and social support, and income generation training. Women were referred to government services for treatment for OIs and other HIV care and antiretroviral therapy (ART).

- At print time, the Population Council was analyzing the results of a study to evaluate referral networks at its sites and whether HIV-positive women accessed the available services and why or why not, and to identify areas for improvement within the referral network.

- At the Microbicides Development Programme Mwanza site, screened-out women may return to access study services but services are limited to counseling and STI management. Most women screened out are older with lower STI incidence. For HIV treatment and other care, these women are referred (without assistance) to local services. Monitoring of the uptake of referrals now takes place.

- The Family Health International Cellulose Sulfate site in Lagos began offering the same referral services to seroconverters as to screened-out women toward the end of the trial. If agreeable, these women were accompanied by staff to the ART clinic for free evaluation and CD4 cell counts. Women who were screened out earlier in the study were traced by outreach workers to encourage them to seek care.

- The Methods for Improving Reproductive Health in Africa (MIRA) trial encouraged screened out women to return for STI results and treatment if needed, and weekly support groups were available. Women were referred to government services or nongovernmental organizations for all needed care but did not receive assistance with required labs.

Trials should consult with government programs and establish formal agreements where possible to avoid the need for repeating HIV and baseline testing and to facilitate access to HIV care and treatment programs when required.

**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 seroconvert should be allowed to stay in the study, and thereby continue to be monitored and receive study-related benefits.
<table>
<thead>
<tr>
<th>HIV prevention trial site</th>
<th>Additional post-test counseling (min. 1 session)</th>
<th>Referral to HIV/ART program</th>
<th>Assistance with referrals</th>
<th>Referral letter to social services or NGO to assist with costs</th>
<th>WHO staging, CD4, OI assessment, prophylaxis, ongoing psychosocial support for duration of study</th>
<th>OI treatment and ART</th>
<th>Pap smear/pelvic exam</th>
<th>HIV care and treatment provided on main study site</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPN 035 Harare, Zimbabwe</td>
<td><img src="checkmark.png" alt="yes" /> <img src="checkmark.png" alt="yes" /> <img src="checkmark.png" alt="yes" /></td>
<td><img src="checkmark.png" alt="yes" /></td>
<td><img src="checkmark.png" alt="yes" /></td>
<td><img src="checkmark.png" alt="yes" /></td>
<td>WHO staging, TB screening</td>
<td><img src="checkmark.png" alt="yes" /></td>
<td><img src="checkmark.png" alt="yes" /></td>
<td><img src="checkmark.png" alt="yes" /></td>
</tr>
<tr>
<td>Population Council Gugulethu, South Africa</td>
<td><img src="checkmark.png" alt="yes" /> <img src="checkmark.png" alt="yes" /> <img src="checkmark.png" alt="yes" /></td>
<td></td>
<td></td>
<td>Can receive from PHC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population Council Soshanguve, South Africa</td>
<td><img src="checkmark.png" alt="yes" /> Support group</td>
<td><img src="checkmark.png" alt="yes" /></td>
<td><img src="checkmark.png" alt="yes" /></td>
<td>Can receive from PHC</td>
<td></td>
<td></td>
<td>Referral</td>
<td><img src="checkmark.png" alt="yes" /></td>
</tr>
<tr>
<td>MDP 301 Umkhanyakude District, South Africa</td>
<td><img src="checkmark.png" alt="yes" /> <img src="checkmark.png" alt="yes" /> <img src="checkmark.png" alt="yes" /></td>
<td></td>
<td></td>
<td>Can receive from PHC</td>
<td>WHO staging, CD4 count, OI assessment</td>
<td><img src="checkmark.png" alt="yes" /></td>
<td></td>
<td><img src="checkmark.png" alt="yes" /> At 1 out of 3 clinics</td>
</tr>
<tr>
<td>MDP 301 Mwanza, Tanzania</td>
<td><img src="checkmark.png" alt="yes" /> <img src="checkmark.png" alt="yes" /></td>
<td></td>
<td>No, but eligible for free STI/family planning drop-in service run by study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><img src="checkmark.png" alt="yes" /> No Pap</td>
</tr>
<tr>
<td>CONRAD Cotonou, Benin</td>
<td><img src="checkmark.png" alt="yes" /></td>
<td>HIV/ART clinic, same location as study clinic</td>
<td><img src="checkmark.png" alt="yes" /></td>
<td>Free</td>
<td><img src="checkmark.png" alt="yes" /></td>
<td><img src="checkmark.png" alt="yes" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIRA Harare, Zimbabwe</td>
<td><img src="checkmark.png" alt="yes" /> <img src="checkmark.png" alt="yes" /></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FHI Cellulose Sulfate Nigeria Site not visited</td>
<td><img src="checkmark.png" alt="yes" /> <img src="checkmark.png" alt="yes" /></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FHI SAVVY** Ghana Site not visited</td>
<td><img src="checkmark.png" alt="yes" /> <img src="checkmark.png" alt="yes" /></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>FHI SAVVY** Nigeria Site not visited</td>
<td><img src="checkmark.png" alt="yes" /> <img src="checkmark.png" alt="yes" /></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ART, antiretroviral therapy; HIV, human immunodeficiency virus; NGO, nongovernmental organization; OI, opportunistic infection; PHC, primary health center; STI, sexually transmitted infection; WHO, World Health Organization.
5.7 Managing Partner-Related Care Issues

Study staff identified partner involvement as a challenge at almost every site visited, with most sites struggling with how to engage male partners effectively in HIV, STI, and risk reduction counseling and services. Furthermore, participants at most sites struggle with how to disclose STIs to their partners and thus risk becoming re-infected if their partners are not treated. Additional issues raised around men included whether or not the study product is safe for men’s use, the role of men in the informed consent process (bearing in mind the high number of partners per participant), and the influence of partners on women’s participation in trials. In this study, we addressed only those aspects of male involvement linked specifically to standards of care issues; namely, HIV testing of male partners, STI testing and treatment, and disclosure of women’s HIV and STI status to their male partners.

There is limited ethical guidance that addresses the male partners of trial participants beyond the requirement in South African guidance that researchers inform participants of how to obtain STI treatment for their partners.* But ethics would require that any involvement of male partners would be done with the women’s consent.

The benefits of engaging male partners are clear. Providing STI testing and treatment for male partners and assisting women with disclosing their status to partners can reduce women’s risk of re-infection and their risk of social harms, such as domestic violence. While some microbicide researchers are making valiant efforts to address the issue of male partners, more could be done.

5.7.1 HIV Counseling and Testing for Male Partners

The availability of HIV VCT for men varied among sites (see Table 12 and Box 16). Some sites provided testing and counseling at the trial clinic itself (CONRAD Benin, HPTN 035 Zimbabwe, MDP Africa Centre, and MIRA), while others provided referrals to

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*South African MRC Guidelines on Ethics for Medical Research: HIV Preventative Vaccine Research Guideline 14.4 (2002) states that “preventive methods should include…treatment of STIs. Simultaneously, participants should be informed how to obtain treatment for their partners.”
existing VCT services in the community (MDP Mwanza and Population Council sites). The FHI CS Nigeria and SAVVY® Nigeria sites did not address the issue of HIV testing of male partners by referral or onsite testing (investigators stated, in part, due to concerns regarding confidentiality). Even where sites offered services for male partners, uptake was generally very low.

Some sites reported they did not offer partner testing because they wanted to protect the confidentiality of female participants, especially those who had multiple partners and would not want partners to meet at the clinic. Other sites noted that men frequently perceive study clinics as women-only spaces, and therefore, are reluctant to seek care there. Still others wanted to avoid putting their counselors in the ethical and legal quandary of knowing the HIV status of both the woman and her partner in situations where the partners had not disclosed to each other.

5.7.2 Sexually Transmitted Infection Testing and Treatment for Male Partners

Similar to HIV testing and counseling services, the availability of STI screening and treatment for male partners varied across trials (see Table 12 and Box 16). Some sites (Population Council, FHI CS) provided male study participants with free STI counseling and treatment but not diagnostic testing, while others provided all three services (MDP Africa Centre, CONRAD, MIRA, HPTN). Some clinicians would also give women an extra dose of medication to take home to their partner(s) if requested. Other sites did not have onsite services for male partners, but at least one provided participants with referrals for care to take to their partners (MDP Mwanza).

For trials targeting high-risk women with multiple partners (e.g., MDP Mwanza), local and international research staff argued that providing testing and counseling at the trial clinic would be complicated by concerns over confidentiality (e.g., jealousy of primary partners upon meeting casual partners). These sites also noted that partner treatment would be relatively ineffective if only some of a woman’s partners were treated. However, as was seen at the CONRAD Benin site, for women with multiple partners, condom use was normally high with casual partners but condom negotiation remained difficult with their steady partners. Therefore, offering services to steady male partners may still prove beneficial.

“Men don’t like anything to do with clinics [or] health care and if they think it has to do with women then they don’t think it has anything to do with them. Getting partners to come in for testing or with [participants] has been a nightmare. VCT here is very poorly taken up, most people who get tested are told to by doctors.”

—STUDY STAFF, SOUTH AFRICA

5.7.3 Disclosure of HIV/Sexually Transmitted Infection Status to Male Partners

Beyond the challenges of providing services to male partners, most study sites recognized a need to provide trial participants with guidance on how to disclose study participation and gel use, HIV serostatus, and STI results to male partners. It is likely that involving men in microbicide trials may help to improve couples’ communication, opening discussion on the question of HIV risk and protection. While some women may fear negative consequences with disclosure, including domestic violence, stigma, and/or loss of relationships, with the proper training, counselors can help participants with decisions around disclosure in the face of these realities. Moreover, male partners’ active support would likely improve overall adherence to the study procedures and encourage women to remain for the full duration of the study.

Clinical trial sites have employed a wide range of strategies to meet the need for preparation and counseling around disclosure of trial participation and clinical results. Most sites counseled study participants on the disclosure of gel use to male partners (HPTN 035, Population Council, MDP, and MIRA) and/or encouraged women to bring their male partners to the clinic or contact the trial to have their questions regarding the trial answered directly by study staff. Box 17 outlines some of the various strategies that sites employed.
**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/sexually transmitted infections; 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.

### 5.8 Non-study Related Care Services

Ancillary care is defined by some as “care which is not required to make a study scientifically valid, to ensure a trial’s safety, or to redress research injuries.” In this report, we take the broader view of the term “standards of care” that is inclusive of elements that may not be study related but are often essential to the well-being of participants (referred to here as non-study related care). The term “ancillary care” implies that such care is an appendage to research rather than acknowledging that the term “standards of care” itself makes it an integral part of what it means to do research ethically in developing countries. At many sites, staff provided some degree of non-study related care, either informally or openly as part of the site-specific SOPs. The amount and types of care provided varied between sites, but even at sites whose study documents explicitly stated that non-study related care would not be provided, study clinicians and staff often provided care unofficially or assisted study participants in accessing referral networks (e.g., establishing partnerships with local clinics or providing transportation if necessary).

The provision of non-study related care continues to be a gray area in research ethics. Ethics guidance tends to be silent on the matter or to imply that the obligation of investigators to attend to the health needs of trial participants extends primarily to the condition under study.
or to injuries or harms arising from the study. One of the most explicit statements about non-study related care is the statement in the commentary to CIOMS Guideline 21: “Although sponsors are, in general, not obliged to provide health care services beyond what is necessary for the conduct of research, it is morally praiseworthy to do so.” This could mean either that there is no moral obligation to provide non-study related care or that the obligation falls on individuals other than the researchers.

In 2006, a group of ethicists and investigators met at Georgetown University in Washington, DC, to explore the boundaries of researchers’ obligations to provide non-study related care within the context of research conducted in developing countries. This group concluded that researchers and their sponsors do have an obligation to provide care beyond that required to conduct the study responsibly or to mitigate harms caused by the research.66

They put forward a series of criteria to help investigators and ethics review committees determine the limits of these obligations, including the degree of unmet need, alternative access to care, and the strength of engagement with participants and the host community. They argued that more explicit guidance is urgently needed: “Leaving the moral burden of assessing ancillary-care claims and the logistical burden of planning for them in the hands of individual principal investigators is unfair, unduly exposing them to controversy and to charges of unethical behavior.”67

Absent such guidance, individual microbicide investigators and clinicians have had to make their own judgments about what non-study related care to provide. They have done so by taking into account a complex array of factors, including:

- Perceived or actual donor restrictions.
- Ethical concerns over “undue inducement” (either real or imagined).
- The skill set of study clinicians (do they have the skills required to provide the care).
- Budgetary constraints.
- The burden such care would place on staff.
- Beliefs regarding what ethics does or does not require.

Box 16

Approaches to Provision of Services for Male Partners

- Uptake for male services, be it HIV testing and counseling or sexually transmitted infection (STI) screening and treatment services, was generally low across trial sites. The Microbicides Development Programme (MDP) Africa Centre study site in Unkhanyakude District, KwaZulu Natal, South Africa, has explored the idea of having open clinic days for men in order to increase uptake, but this plan was not yet implemented at the time of our visit.

- Everyone was eligible for STI services at the Contraceptive Research and Development (CONRAD) Cellulose Sulfate study clinic in Benin. The primary study clinic successfully developed separate services for men during Projet Sida, and while funding for separate services was no longer available during the CONRAD trial, about 12 men per day continued to be seen for HIV or STI care at the regular clinic.

- Male partners at the MDP Mwanza site were referred by letter to Seke Toure Regional Hospital for STI screening and treatment. When the staff followed up to assess male uptake of referral services offered, they found that 22 out of 30 men had presented for treatment. Despite study sponsor and staff concerns that offering services to male partners directly (not through referral) would be problematic or ineffective, many of the women at the MDP Mwanza site—the majority of whom have multiple partners—identified STI services for their partners as a critical need and continued to ask researchers to provide them directly. Although the site explored the idea of offering male partners free STI services, this plan was not implemented at the time of our visit, as study staff felt that referral to existing services was more sustainable. Existing services, however, are overburdened and typically require long waits.
While the standards of care advisory group did not come to consensus on any specific recommendations related to non-study related care, the mapping exercise revealed that trial sites do provide some types of non-study related care. The field clearly needs further discussions about how to establish the proper boundaries of that care and a process for engaging local stakeholders in this discussion.

**5.8.1 Findings: Non-study Related Care**

Across the trials reviewed as part of this exercise, most study-wide documents explicitly stated that non-study related care would not be provided by the study or were silent on the issue. Those that addressed the issue often maintained that if a study participant presented with a non-study related health concern, the clinical staff would refer the participant to community-based medical clinics or hospitals, depending on the severity of the ailment. Costs of treatment for non-study related medical problems are generally borne by the participant or by a third party (e.g., local or national government). An exception to this is the MDP trial, budgeted specifically for the provision of non-study related care. Local MDP sites have the freedom to stock medications that they think they will need, depending on local health concerns. For instance, in areas where malaria is endemic, the site may stock and provide participants with anti-malarial medication. For sites that are already embedded in existing care facilities, like the MDP Africa Centre site in KwaZulu Natal, routine provision of non-study related care is relatively easy, as study clinicians are free to use DoH supplies to treat ancillary care concerns (see Box 18).

Despite overwhelming statements in study documents that staff would not provide non-study related care, study staff reported many examples of clinicians providing or paying for non-study related care, sometimes at their own expense (see Table 13). Staff at many research sites believed that providing non-study related health services benefited both study participants and study outcomes. Non-study related care improves overall follow-up and retention by encouraging women to come for study visits rather than spend time and money seeking needed care elsewhere. As a staff member at one Population Council site commented, “We don’t have a problem treating… simple infections. [If a study participant has] a headache, flu, [and] she wants to be onsite, she wants to be here, we don’t want her to miss her date. So if the doctor is here and we can treat, we don’t mind.”

Other researchers argued that non-study related care falls outside of legitimate study-related costs, or they felt uncomfortable providing care that is outside their realm of expertise.

**Approaches to Male Partner Involvement and Disclosure**

- At the Population Council’s Gugulethu site, study staff asked participants to obtain permission from their male partners for the study to contact them by telephone to answer questions about gel and condom use and overall study participation. If a woman’s partner agreed to be contacted, the study participant would give her partner’s contact information to a study counselor who would then call him directly to answer any questions.
- The Microbicides Development Programme Africa Centre (MDP) site has considered training one counselor to be a disclosure counseling expert as a resource for participants and other study counselors.
- The Methods for Improving Reproductive Health in Africa (MIRA) site in Harare drafted plans to provide counseling for men and couples and to encourage male involvement through targeted outreach, by offering male and couples counseling during special hours, and by providing letters of excuse to employers. The plans, however, were never fully implemented, due in part to perceived lack of interest from male partners.
In general, study investigators and trial sponsors interviewed were unclear about whether they have an ethical obligation to treat medical conditions unrelated to the goals of the study, but at the site level, staff clearly felt the need to do so. One international study coordinator articulated the tension everyone feels between providing care and doing research: “We all want to provide as much care as possible, but don’t want to provide so much that we burden the research staff and diminish the quality of care provided in the trial—at the end of the day, we want to answer our study questions.”

**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.

**Approaches to Provision of Non-study Related Care**

- **At the Microbicides Development Programme (MDP) site in Unkhanyakude District, KwaZulu Natal, South Africa,** study staff openly provide non-study related care. The study sites, located next door to Department of Health (DoH) public health clinics, recruited patients from the clinics. During recruitment talks in the public health clinic waiting rooms, study staff offered patients interested in learning more about the trial to have the care they needed provided at the study clinic before receiving more information about the trial (there is typically a long wait at DoH clinics). Non-study related care was also provided for study participants and their families (sick and well child care) using DoH-provided resources and supplies (e.g., if a child was scheduled for immunization, study staff would walk to the public health clinic, take the vaccine, and give it to the child on behalf of the clinic, documenting the care in the DoH clinic register). As the public health clinics are understaffed and crowded, they benefited from study nurses lightening their load. In turn, the study benefited by easy access to their target population, and women benefited from easier access to needed primary health services. There is little conflict between local and research standards of care, as the study provided all care according to national guidelines and using nationally purchased commodities (also a savings to the study).

- **At the MDP Mwanza site in Tanzania,** almost no non-study related care was provided, in part because of the study population (mobile, multiple partners), and in part because of how the study was implemented. Study-related care was provided at eight mobile clinic sites in hotel rooms rented for one half-day per week, and staff transported all study supplies with them twice daily to be set up and taken down. Transport limited the amount of equipment, medicines, and medical staff that the study was able to provide during study clinics.

- **At the HIV Prevention Trials Network (HPTN) 035 study site in Harare, Zimbabwe,** study participants often presented at the study clinic with non-study related health concerns as a result of their familiarity and comfort with the study staff, as well as the erratic and chaotic nature of health care services in the current economic and political climate. Staff at this site provided diagnosis and/or treatment for a limited number of non-study related health concerns (e.g., malaria, diarrheal diseases, minor respiratory infections, dermatological conditions, and minor psychosocial problems), and the study tried to keep a supply of antibiotics and other medications on hand at all times.

- **Study staff at the Population Council site in Gugulethu** provided reproductive health talks and demonstrations on breast health in the clinic waiting room. They also provided breast exams, referring women with abnormal findings to a local public health clinic and assisting participants in accessing referral networks by making appointments and providing transportation if necessary. As the site was near other public health clinics where free care was provided, staff reported that they did not feel compelled to also provide these non-study related health services.
5.9 In-country Capacity-Building

Given the need to establish state-of-the-art laboratory facilities and to train local staff, some amount of capacity-building occurred at every microbicide trial site.

Many guidance documents highlight the need to improve local health care infrastructure and community-level public health programs, either directly or through partnerships with host-country organizations.68 The South African ethics guidance states that “local standard of care in the host community should be improved with a contribution of lasting benefit [and] community representatives should play a key role in determining how such capacity is built.”69 Many microbicide trials have conscientiously made strides to strengthen local health care services and the capacity of local research staff. Some of the best examples of capacity-strengthening that we observed were possible

<table>
<thead>
<tr>
<th>HIV prevention trial site</th>
<th>Non-study related care provided, per protocol/study documents</th>
<th>Non-study related care provided, per site visit and staff interviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONRAD Cotonou, Benin</td>
<td>Study clinic located in public health hospital; most health care provided by study staff or at the public health clinic of the hosting hospital, next door, where women are required to pay for services; sometimes staff helped indigent women pay for needed care out of pocket.</td>
<td></td>
</tr>
<tr>
<td>HPTN 035 Harare, Zimbabwe</td>
<td>Study staff try to treat and/or refer where possible. Women prefer to come to the study because they are familiar with the staff and do not pay for treatment (when it is available). Clinic staff sometimes help get care for participants and family (anecdotal from clinic staff). Diagnosis and treatment of malaria, chest x-ray, treatment of respiratory infections and skin problems if able, can send stool for persistent diarrhea.</td>
<td></td>
</tr>
<tr>
<td>MIRA Harare, Zimbabwe</td>
<td>Referred to medical services and other sources available in the community.</td>
<td></td>
</tr>
<tr>
<td>Population Council Gugulethu, South Africa</td>
<td>If a woman presented with health concerns, the clinician would write medical referral; study staff made referral appointments, sometimes transportation was provided if a driver was available (or ambulance could be called); study tried to keep stock of medications, limited; had emergency drugs to stabilize patients while waiting for ambulance; at times, treated for minor problems such as UTI.</td>
<td>Occasion for minor problems (for UTIs, could do dipstick and treat according to SOPs). Referrals for all other health problems; study staff made appointments; sometimes transportation was provided. Emergency medicines were available if needed. Other health issues referred to hospital for treatment. One nurse reported that if the doctor was in and the study had the treatment, they could treat non-study related concerns.</td>
</tr>
<tr>
<td>MIRA Harare, Zimbabwe</td>
<td>Referred to medical services and other sources available in the community.</td>
<td></td>
</tr>
<tr>
<td>Population Council Soshanguve, South Africa</td>
<td>If a woman presented with health concerns, the clinician would write medical referral; study staff made referral appointments, sometimes transportation was provided if a driver was available (or ambulance could be called); study tried to keep stock of medications, limited; had emergency drugs to stabilize patients while waiting for ambulance; at times, treated for minor problems such as UTI.</td>
<td>Referred to medical services and other sources available in the community.</td>
</tr>
<tr>
<td>MDP 301 Unkhanyakude District, South Africa</td>
<td>Malaria was most often seen. Doctors would diagnose and write a prescription for participants for this and other ancillary health conditions.</td>
<td>Malaria was most often seen. Doctors would diagnose and write a prescription for participants for this and other ancillary health conditions.</td>
</tr>
<tr>
<td>MDP 301 Mwanza, Tanzania</td>
<td>If a woman presented with health concerns, the clinician would write medical referral; study staff made referral appointments, sometimes transportation was provided if a driver was available (or ambulance could be called); study tried to keep stock of medications, limited; had emergency drugs to stabilize patients while waiting for ambulance; at times, treated for minor problems such as UTI.</td>
<td>If a woman presented with health concerns, the clinician would write medical referral; study staff made referral appointments, sometimes transportation was provided if a driver was available (or ambulance could be called); study tried to keep stock of medications, limited; had emergency drugs to stabilize patients while waiting for ambulance; at times, treated for minor problems such as UTI.</td>
</tr>
<tr>
<td>FHI Cellulose Sulfate Nigeria Site not visited</td>
<td>Referred for further treatment if needed; the study did not cover the cost or provide drugs for ancillary health conditions.</td>
<td>Site not visited. Study clinicians would write prescription or recommend a drug or refer for hospitalization if necessary. Malaria was most often seen. Doctors would sometimes diagnose and write a prescription for participants for this and other minor problems. *</td>
</tr>
<tr>
<td>FHI SAVVY® Nigeria and Ghana Site not visited</td>
<td>Site not visited.</td>
<td>Site not visited.</td>
</tr>
</tbody>
</table>

DoH, Department of Health; OI, opportunistic infection; SOP, standard operating procedure; STI, sexually transmitted infection; UTI, urinary tract infection.

* Per interview with country-level investigator.
because of the site’s close proximity to local care facilities.

GCM maintains that researchers and donors should use HIV trials as an opportunity to incrementally improve local standards of care and seek ways to do so in a sustainable fashion when designing trials. In order to build capacity, as well as support existing services and facilitate easier access to referral services for study participants, trials should seek opportunities to co-locate or partner with existing local care facilities.

5.9.1 Approaches to Capacity-Building

Most of the study staff interviewed thought of “capacity-building” in terms of improving local research infrastructure, rather than providing wider benefits to the community. When queried on capacity-building, respondents mentioned training of local study staff; the building, renovation, and/or staffing of clinics and laboratories (including space sometimes shared with local public health facilities); educational outreach in the community; and the purchase of essential equipment and supplies—from vehicles and computers to laboratory diagnostics and latex gloves. With the exception of community education and raising awareness of HIV and AIDS, these capacity-building efforts improve the local research infrastructure but generally do not lead to improvements in local public health care systems (see Box 19 for examples of how some sites approached capacity-building).

Staff argued that research efforts provide significant indirect benefits to host communities. Well-trained research staff may return to the public sector, employing their improved skills. Research exposes study participants and site-level staff to higher quality, more patient-centered health care. The focus in trial clinics on prevention and early identification of health problems such as STIs and cervical dysplasia introduce both providers and participants to the notion of preventative health care, rather than focusing solely on managing symptoms.

The recent expansion and availability of HIV/AIDS care and treatment services has created opportunities for trial sites to form mutually beneficial partnerships with local agencies to simultaneously conduct high quality research while improving care for participants and communities. As local priorities vary from site to site, so too will the approaches for addressing capacity-strengthening needs. Sites can address the issue of sustainability by involving local partners in the conceptualization and implementation of any improvements.

> 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.

5.10 Community Involvement in Care-Related Issues

All of the microbicide trial sites that we visited engaged in some form of community involvement. Sites differed in the structures and strategies they employed (see Box 20), and most did not have specific strategies for engaging communities in care-related decision-making. However, many were attempting to increase the level of engagement with the surrounding host communities and larger civil society structures—and many had seen the benefits of having good community relations when faced with questions about the conduct or premature closing of a trial (see Case Study 5). Ethical guidance documents generally stress community involvement as essential to the ethical conduct of trials. The UNAIDS/WHO guidance, Ethical Considerations in HIV Biomedical Prevention Trials, notes: “To ensure the ethical and scientific quality of proposed research, its relevance to the affected community, and its acceptance by the affected community, community representatives should be involved in an early and sustained manner in the design, development, implementation, and distribution of results….”70 Most sites had formal or informal community advisory groups and at least some staff dedicated to working with the community.
Additional UNAIDS/WHO guidance points call upon investigators to seek community input when making critical care-related decisions. Guidance Point 14, for example, argues that “prior to initiation of a trial,” investigators should “come to agreement through participatory processes on mechanisms to provide and sustain such HIV-related care and treatment.”

From our observations, this kind of dialogue is still rare. At all sites except MDP’s Africa Centre, community members and advisory groups were not consulted about what prevention or care should be part of the studies before protocols were approved, but were sometimes asked to comment after the protocol had already gone through the approval process. Ongoing community engagement processes continued to raise issues related to standards of care, most frequently regarding access to treatment and care for people who become HIV-positive during the trial, access to care for partners and family members, and continued post-trial access to care.

As noted, many sites did not have mechanisms in place to seek community input on care-related benefits. This can lead

**Approaches to Capacity-Building**

- Each of the three Population Council sites had a lump sum (approximately 100,000 USD) budgeted to assist in the care of seroconverters. At the Gugulethu site, researchers discussed with the Department of Health (DoH) how to best use this money, electing to support an additional HIV clinic every week at the busiest public health center. At the Setshaba site, the money was used to finance medical services and an HIV support and care group for seroconverters and women who screened out as HIV-positive. Discussions about continued funding for the group through the US President’s Emergency Plan for AIDS Relief (PEPFAR) or transfer to a local nongovernmental organization were ultimately unsuccessful.

- The Microbicides Development Programme (MDP) KwaZulu Natal site benefited from being associated with the Africa Centre, an already established research facility and administrator of the district PEPFAR grant. The MDP study physician dedicates one day per week to the Africa Centre-run PEPFAR HIV program at one of the local DoH clinics, and it was planned for study counselors to work in the antiretroviral therapy program once a week, although this never occurred due to scheduling conflicts. The study site had strong links to local DoH-run primary health centers, allowing study nurses to provide participants with complete non-study related health care services, including child immunizations and dispensing of DoH-provided medications. MDP has also supported DoH clinics by providing clinic walls and storage locks and the occasional loaning of equipment. The site trained all research nurses in the prescribing and dispensing of antiretrovirals and other medications and in advanced family planning so that study nurses are better equipped to return to the public sector once the trial ends. In addition, Africa Centre staff were eligible to receive funds (R4,000) toward master of science courses at the University of KwaZulu Natal, and MDP agreed to fund postgraduate programs for key staff. Specific trainings by MDP and Africa Centre staff were also offered to DoH staff.

- At the MDP site in Mwanza, mobile study clinics were run out of area hotels. Hotel rooms were rented for one half-day per week, and study equipment was transported to and from the hotel by the study staff. This implementation structure made it easier for some participants to attend the clinic for scheduled and unscheduled visits (many of the women work out of these hotels), but also limited the partnerships and capacity-building in which the study was able to engage. The study did partner with the local DoH system by prescribing and dispensing DoH contraceptives to study participants, but other opportunities for capacity-building and partnerships were inherently limited.
to tensions around community expectations in terms of what is possible and appropriate within the context of a trial. Community members tended to view researchers as “wealthy,” and frequently hoped and expected they would provide a greater range of benefits than research dollars could support. In addition, they have, justifiably, begun to demand that research has direct benefits to their community regardless of study outcomes.

**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.

**GCN 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.

### Approaches to Community Input

- The Community Advisory Board at the Microbicides Development Programme (MDP) Africa Centre site advised on all studies run out of the Africa Centre, and had a dedicated representative responsible for the microbicide trial. The Board reviewed and commented on research proposals before they became protocols and before they underwent ethics review. The Africa Centre and MDP study staff also consulted with local tribal leaders (indunas), and attended community meetings.

- There were no community advisory boards at the Nigerian sites, but investigators established relationships with various community members.

- Population Council sites in Gugulethu and Soshanguve utilized a traditional community advisory board structure to engage the community in the research process. The Population Council’s Durban site did not establish a board because of ethnic and political divisions that made it difficult to organize a productive group of community representatives. Instead, the site organized individual meetings with various stakeholders and held larger community updates once a year.

- There was no community advisory board at the Contraceptive Research and Development (CONRAD) site in Benin, but peer outreach workers (some of whom were former or current sex workers) were involved in designing services that CONRAD took over when implementing the Cellulose Sulfate study. As a result, these services appeared to meet most of the reproductive health needs, and all of the HIV prevention and care needs, of study participants and their community. Participants provided ongoing feedback to peer outreach workers, who held regular meetings with women, men, and brothel owners.

- The HIV Prevention Trials Network (HPTN) 035 site in Zimbabwe had a community department that conducted a community mapping at the start of the trial, continued to work with community members and leaders throughout the trial, promoted education/awareness, and assisted with participant recruitment, participant retention, and other study implementation issues. The study also held bimonthly community advisory board meetings and frequent local stakeholder meetings.
5.11 Care for Research-Related Harms

All of the sites conducting microbicide trials had plans in place for dealing with physical injuries that might arise as a direct result of study participation. Few sites, however, had written policies or procedures for providing financial compensation or long-term chronic care for study-related harm, or formal policies or procedures for dealing with social harms that may arise as a result of study participation (see Box 21).

When considering the issues that surround research-related harms, it is important to keep in mind the following four distinctions:

1. What are the ethical versus legal obligations of study investigators and sponsors?
2. Are investigators and sponsors only required to provide treatment for a study-related injury, or should they also consider compensation for harm?
3. What is the obligation to provide acute versus long-term care for research-related injuries?
4. What is the responsibility of researchers to minimize the risk of physical versus social research-related harms?

When a study participant is harmed as a direct result of participation in a research trial, investigators and sponsors are ethically obligated to provide the subject with medical care, or in some cases, financial compensation. In the case of an experimental compound like a microbicide, product developers also have an ethical and (sometimes) a legal responsibility to provide compensation for product-related harms, and most developers carry insurance to cover these expenses. However, the obligation to provide long-term chronic care or compensation and/or care for non-study related or social harms remains unclear.

Some guidance documents state that research participants are entitled to treatment and compensation for any research-related injury, but these aspirational guidance documents do not carry the force of law. Rather, national and international regulations grant researchers, institutions, and sponsors considerable leeway concerning treatment and compensation for research-related injuries. Harm-related claims are likely to be dealt with on a case-by-case basis, in accordance with institutional, sponsor, or local policies.

US Federal Policy for the Protection of Human Subjects (also known as the “Common Rule”) governs research with human subjects conducted or supported by US federal departments and agencies, including the NIH. Although the Common Rule requires that study participants be told what types of compensation or treatment will be available if a research-related injury occurs, there is no legal requirement to provide treatment or compensation. In contrast, both South Africa and Zimbabwe require clinical research sites to carry liability insurance to cover the cost of treating a research-related physical harm. The South Africa Medicines Control Council, for example, requires that participants be covered by comprehensive insurance for injury and damage. Similarly, the Medicines Control Authority of Zimbabwe requires that all study sites carry insurance to cover research-related harms.

In terms of physical injuries, each site investigator is responsible for determining the relationship of any adverse event to study participation, with essential short-term medical care and treatment provided to study volunteers free of charge (either at the study clinic, or if necessary, by referral for tertiary care). Investigators must report study-related adverse events to international study coordination centers and sponsors, and local health, regulatory, and ethics review committees. No site had an example of a study-related harm that had arisen. Despite clear precedent, it seemed likely that most study sites would pay for costs of acute treatment for study-related biomedical harms—either providing it themselves or by paying the cost of referral. Most protocols also stipulated that treatment for non-study related harms (adverse events and serious adverse events not directly linked to product use) would not be covered, but we found several examples of non-study related harms where the study did cover (partially or in full) health care expenses for a participant’s medical problem.

Clinical researchers and trial sponsors have a responsibility to also address research-related social harms (i.e., non-medical adverse events) resulting from microbicide trial participation by developing strategies to prevent or
minimize any adverse consequences of HIV prevention research. Although the concept of social risk parallels the concept of physical risk, few sites had formal policies or procedures for dealing with psychological, social, and economic harms that may arise from study participation. Some sites (HPTN 035 and Population Council), however, recognized the psychosocial and economic risks associated with HIV prevention research, and developed procedures and practices designed to mitigate such harms (see Case Study 6).

- At the HIV Prevention Trials Network (HPTN) 035 site in Harare, Zimbabwe, study staff worked with study participants to design and implement “strategies...to address the problem” when a social risk or harm was reported. Other than a few anecdotal reports of domestic violence handled by referral to public psychosocial services, however, no examples of how staff dealt with study-related social harms were available after the fact. Significant effort was made to identify risk of social harm by counselors and other staff at all study visits and to prevent or mitigate it.

- At Microbicides Development Programme (MDP) sites, the product developer (Indevus Pharmaceuticals, Inc.) assumed liability for product-related harms in accordance with written agreements with the study sponsor. The study sponsor, the British Medical Research Council, was responsible for resolving any issues of responsibility for harms not related to the product or clinical negligence.

- Study staff at the MDP Africa Centre site reported that partner violence was a significant problem, with three women having withdrawn from the study as a result of partner opposition. One woman, whose partner encouraged her participation until his friends raised concerns over infidelity, was beaten and her supply of study gel burned. This particular participant stopped using gel but stayed in the trial for follow-up. Participants could talk about domestic violence and other social issues with study staff, and counselors could refer women to psychosocial services (such as the psychiatry department at Hlabisa Hospital and two local, small support groups run by community-based organizations), but staff expressed the desire for increased training and guidance on how to deal with such issues.

### Approaches to Research-Related Harms

#### Case Study 6: HPTN 035

At the HPTN 035 site in Harare, Zimbabwe, study staff worked with study participants to design and implement strategies...to address the problem” when a social risk or harm was reported. Other than a few anecdotal reports of domestic violence handled by referral to public psychosocial services, however, no examples of how staff dealt with study-related social harms were available after the fact. Significant effort was made to identify risk of social harm by counselors and other staff at all study visits and to prevent or mitigate it.

#### Case Study 7: MDP Africa Centre

At the MDP Africa Centre site, significant effort was made to identify risk of social harm by counselors and other staff at all study visits and to prevent or mitigate it.

### 5.12 Post-trial Access to Study Products

Few of the sponsors conducting clinical trials of candidate microbicides had set policies for facilitating post-trial access to products, although some had explored strategies for maintaining access for participants after the trial (see Box 22). Even if a trial demonstrates that a product is effective, it could take several years before regulatory agencies approve it for widespread distribution. In such circumstances, investigators could arrange to continue importing and supplying product to former trial participants on a "named basis." In some instances, products that are not yet approved by regulatory authorities can continue to be given to former trial participants by submitting a list of those who will be using the unapproved product (i.e., on a "named basis"). Alternatively, investigators could provide product within the context of "introductory studies" that are...
designed to explore critical questions such as how to deliver the product most effectively.

Ethics guidance generally maintains that those who participate in clinical trials should receive continuing access to effective experimental products. Although this central tenet of research ethics is enshrined in guidance such as the WMA’s Declaration of Helsinki and CIOMS’ International Ethical Guidelines for Biomedical Research Involving Human Subjects, ensuring post-trial access to new products can be difficult in practice, given the economic and regulatory hurdles that often arise.74,75 The Declaration of Helsinki also says that plans for post-trial access must be described in the study protocol so that ethics committees may consider it in their reviews.76 Despite this provision, none of the protocols reviewed as part of this exercise specifically addressed the issue.

### 5.12.1 Approaches to Planning for Post-trial Access

While local stakeholders sometimes broached issues of post-trial access, the majority of discussions around access to product after trials end have occurred at higher levels—between international sponsors, donors, regulatory authorities, and pharmaceutical companies and manufacturers. Some networks and organizations conducting trials (HPTN 035, Population Council, and MDP) explored options for future access to product in the countries where trials were being conducted, including discussions with in-country regulatory authorities, exploration of local manufacturing capacity, and the potential design of introductory studies as a bridge between proven effectiveness (if applicable) and approval by regulatory authorities.

**Approaches to Post-trial Access to Products**

- At the time of analysis, the HIV Prevention Trials Network (HPTN) 035 protocol team had discussed with product developers (ReProtect and Indevus) licensing agreements and preferred pricing arrangements to ensure affordable access in resource-poor countries. They were also planning to initiate discussions with other public and private funding sources (e.g., the World Health Organization, the Joint United Nations Programme on HIV/AIDS, and the Bill & Melinda Gates Foundation) to purchase product in bulk and offer it at low or no cost to the study communities, as well as to conduct operations and marketing research to maximize acceptability and use in at-risk populations.

- Before study closure, the Population Council established formal procedures to inform study participants and the public about trial results, including a toll-free phone number to provide study participants with updates and possible one-on-one meetings with study participants at the trial’s end to “unblind” them, and used community meetings and media advertisements to disseminate research findings. The Population Council also began preliminary negotiations with local companies about licensing and large-scale manufacture of product, although in the end, the product (Carraguard®) did not show an effect against HIV.

- The Microbicides Development Programme (MDP) held discussions with South African regulatory bodies and Indevus to explore issues of approval, licensing, and economically reasonable modes of product distribution and delivery. The MDP site in Mwanza, Tanzania, which is scheduled to close considerably earlier than other MDP sites, also planned to trace study participants every three months so that they could be contacted for enrollment in any future Phase 4 studies. Site staff planned to develop and distribute an information sheet with information about the possibility of future Phase 4 studies.

- As part of the Methods for Improving Reproductive Health in Africa (MIRA) study, Ibis Reproductive Health held meetings with in-country regulatory authorities and planned to meet with local governments and other stakeholders to discuss issues of post-trial access. Study participants were allowed to keep the MIRA-provided diaphragm (or were provided with a new one) for contraceptive purposes only, and participants in the control arm received a diaphragm when the trial ended. At the time of analysis, Phase 3b/4 studies were being planned to look at the feasibility of diaphragm/gel as a sustainable intervention to prevent HIV but were not implemented when the intervention showed no efficacy.
5.13 Continuity Post-trial

Most ethics guidance does not discuss participants’ continued access to care after a study ends, other than access to the experimental product should it prove effective. 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.

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.

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 CS site provides an enlightening example of what can happen despite clear efforts to address continuity of care issues up front. As described earlier (Case Study 3, Care and Treatment for HIV at the Contraceptive Research and Development Site, Cotonou, Benin), 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.

““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

Consensus Recommendation: Future trials should seek opportunities to co-locate or partner with existing local care facilities in order to 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
nongovernmental organizations 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:** Trial sites need to develop concrete plans surrounding trial closure, including plans for transitioning all trial volunteers into public health sector or nongovernmental organization-provided services, and providing formal acknowledgment 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.

**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.

**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 nongovernmental organization), 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.

### 5.14 Influence of Donor Policies

As part of the mapping, we also explored the potential effects that donor policies could have on standards of care. In our review, we found no binding policies that establish standards of care for trial participants, but we did find examples of where specific policies or uncertainty over donor policy affected care-related decision-making. In particular, U.S. Government donor policies have created confusion and influenced decisions regarding care, including:

- Requirements governing US-funded family planning activities, including abortion-related restrictions.
- Requirements on HIV/AIDS activities funded under PEPFAR, including a provision related to condom information and restrictions relating to prostitution and sex trafficking.
- NIH and CDC-specific restrictions on ability to construct new facilities in foreign countries.
- NIH-specific restrictions on use of funds for drugs and non-research related care.

**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.
In addition to the specific, care-related domains explored in the mapping exercise, we encountered three themes that infused many of our standards of care conversations:

**Stigma**

Stigma about HIV was a pervasive theme in all of the communities that we visited. It limited women’s willingness to volunteer for trials (because they were afraid of testing HIV-positive), their willingness to disclose their status to partners and family members, and their willingness to seek care. Stigma was no less common among clinic staff than among trial participants. In all of our travels, we met only one staff member who openly acknowledged being HIV-positive. Sites did try to implement policies to limit stigma—for example, giving all screened women a similar-looking referral note, regardless of the results of their HIV tests. But additional anti-stigma work and values clarification training could help staff both accept their own status and become true leaders in the community in combating stigma.

**Undue inducement**

Concern over “undue inducement” was a second theme that pervaded discussions on standards of care. Many investigators and staff cited uncertainty around “undue inducement” as relevant to the decision of whether or not to provide certain services. The fear was that by providing services not available locally, the trial might actually undermine informed consent by presenting potential participants with an offer too good to refuse.

The issue of undue inducement is a valid concern in research ethics, but one that is often misunderstood. The issue is not whether there is inducement—inducements pervade everyday life—but whether the offer encourages individuals to accept a risk that someone else, in less difficult circumstances, would refuse to accept. The key element is the assumption of unreasonable risk, due to a contextually defined vulnerability. For example, it is perfectly acceptable for employers to offer higher salaries and better vacation plans to “induce” an individual to accept employment. What is not acceptable is when a similar offer encourages an individual to go against his or her own best interests.

Concern over “undue inducement” was one of the early arguments advanced against providing access to ART for those who seroconvert in trials. But more recently, ethicists have argued that such concerns are misplaced, as long as the risk of the overall trial is acceptable. As Emanuel and colleagues observe: “Undue inducement requires offering something valuable that leads to both bad judgments and exposure to unreasonable risks…. Tempting offers in desperate situations that have clear good results are not undue inducements.”77 In general then, if the risk-benefit ratio of a trial is positive, it is ethically acceptable if participants volunteer to participate in part to gain access to better health care services than they could access outside of the trial. Ultimately, it is the responsibility of ethics review boards (international and local IRBs) to ensure that trial design and implementation pose minimal risks to participants.

While some ethicists caution against categorically dismissing concerns about...
“There is a big difference between care in [the] trial and outside—the personal contact, staff is not overworked or underpaid. In the public sector patients show up and wait all day. Nurses and counselors want to see patients as quickly as possible. In the study, relationships are built.”

—STUDY PSYCHOLOGIST, SOUTH AFRICA

undue inducement, the general sense is that undue inducement should not be a barrier to ratcheting up standards of care. Indeed, accepting reasonable risk and some inconvenience in order to gain access to improved care could be a rational decision for rich and poor participants alike.

**Referral as a mechanism for accessing care**

A final overarching theme was the challenge of relying on referral as the primary mechanism for ensuring access to care. Virtually all sites noted the limitations of referral—the overcrowded public facilities, lack of trained staff, long waiting lines, and bureaucratic red tape. They likewise noted the difficulties women face in actually accessing care—concerns over stigma, problems with transport, the costs of care, and competing priorities for scarce time and resources. Most sites realized early on that simply referring women to available services was not adequate. Women did not show up.

The reasons here are complex. Often women who become HIV-positive still feel well and do not perceive themselves in need of services. There are also psychological, physical, and economic barriers to women pursuing care. Most sites have revisited their referral strategies and are now trying to facilitate help-seeking where possible. Two trials, MIRA and the Population Council’s Carraguard® study, implemented studies to examine barriers to accessing needed care and how to improve their referral systems. At all sites, staff now visit referral centers to clarify services offered, to make themselves and the study known to referral staff, and to make informal, or where possible, formal agreements about the care that is offered.

These trials confirm what has been known for decades from other fields: unassisted referral seldom results in clients accessing care. Referral will likely remain a central component of systems to access care established at trial sites, but much more can be done to facilitate referral, including accompaniment programs, subsidized transportation, assistance with red tape, building stronger in-person linkages with referral staff, etc. The next generation of trials should build on the experience from the HIV prevention trials that have gone before, as well as from the fields of maternal health, domestic violence, and family planning, when designing and implementing referral systems.
7.0 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 ART 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.
Many of the study participants at the MDP Mwanza site worked preparing food for sale and/or worked in traditional bars preparing and selling local beer.
Appendix I. Consensus and Author Recommendations

The recommendations in this report marked with ➔ and HIGHLIGHTED IN BLUE BOLDFACE are “consensus recommendations” that emerged from a consultation convened by the Global Campaign for Microbicides in Johannesburg, South Africa, June 11–12, 2007. The recommendations marked with ★ and HIGHLIGHTED IN GRAY BOLDFACE are “authors’ recommendations” that emerged after the consultation as the Global Campaign for Microbicides (GCM) continued its thinking and discussions and refined its conclusions.

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<th>Consensus Recommendation</th>
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<td><strong>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.</strong></td>
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<td><strong>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.</strong></td>
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<td><strong>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.</strong></td>
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<td><strong>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.</strong></td>
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<td><strong>Future trials should seek opportunities to co-locate or partner with existing local care facilities in order to 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 nongovernmental organizations or public clinics to build up their services at the beginning of a trial could help address long-term care needs after trial closures.</strong></td>
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<td><strong>The female condom should be integrated into the standard prevention package in future and ongoing trials, and provided by sponsors at research sites even when 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.</strong></td>
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<td><strong>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.</strong></td>
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<td><strong>Future trials should pursue concrete steps to improve referral systems and facilitate access to government or nongovernmental organization-run HIV/antiretroviral therapy programs for women who screen HIV-positive at enrollment by providing World Health Organization 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 to facilitate access to HIV care and treatment programs when required.</strong></td>
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<td><strong>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 visual inspection of the cervix with acetic acid wash (VIA) where they are approved.</strong></td>
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<td><strong>Laboratory screening and treatment for sexually transmitted infections, 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.</strong></td>
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<td><strong>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.</strong></td>
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<td><strong>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.</strong></td>
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</tbody>
</table>
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 staff's HIV status in the same manner they protect trial participants.

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.

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.

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

Women who seroconvert should be allowed to stay in the study, and thereby continue to be monitored and receive study-related benefits.

Trial sites need to develop concrete plans surrounding trial closure, including plans for transitioning all trial volunteers into public health sector or nongovernmental organization-provided services, and providing formal acknowledgment 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.

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 nongovernmental organization), 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.

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.

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.

Every effort should be made by researchers to build capacity and infrastructure to strengthen sexually transmitted infection (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.

To build program capacity and contribute to improved sexually transmitted infection (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.

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.

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 men; decrease potential social harms; provide at least minimal services to men to increase their knowledge of HIV/sexually transmitted infections; 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.

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.

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.

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)

<table>
<thead>
<tr>
<th>Participant name</th>
<th>Affiliation</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khatija Ahmed</td>
<td>University of Limpopo/Setshaba Research Centre</td>
<td>South Africa</td>
</tr>
<tr>
<td>Deborah Barron</td>
<td>Consultant, Global Campaign for Microbicides (GCM)</td>
<td>South Africa</td>
</tr>
<tr>
<td>Manju Chatani</td>
<td>African Microbicides Advocacy Group (AMAG)</td>
<td>Ghana</td>
</tr>
<tr>
<td>Anne Coletti</td>
<td>Family Health International (FHI)</td>
<td>United States</td>
</tr>
<tr>
<td>Dazon Dixon Diallo</td>
<td>SisterLove</td>
<td>United States</td>
</tr>
<tr>
<td>Zaynab Essack</td>
<td>HIV/AIDS Vaccines Ethics Group (HAVEG)</td>
<td>South Africa</td>
</tr>
<tr>
<td>Michelle Folsom</td>
<td>PATH</td>
<td>South Africa</td>
</tr>
<tr>
<td>Barbara Friedland</td>
<td>Population Council</td>
<td>United States</td>
</tr>
<tr>
<td>Mitzy Gafos</td>
<td>Africa Centre/Microbicides Development Programme (MDP)</td>
<td>South Africa</td>
</tr>
<tr>
<td>Lori Heise</td>
<td>Global Campaign for Microbicides (GCM)</td>
<td>United States</td>
</tr>
<tr>
<td>Pauline Irungu</td>
<td>Global Campaign for Microbicides (GCM)</td>
<td>Kenya</td>
</tr>
<tr>
<td>Naomi Lince</td>
<td>Ibis Reproductive Health</td>
<td>South Africa</td>
</tr>
<tr>
<td>Margaret Mlingo</td>
<td>University of Zimbabwe-University of California, San Francisco (UZ-UCSF)</td>
<td>Zimbabwe</td>
</tr>
<tr>
<td>John Mutsambi</td>
<td>Global Campaign for Microbicides (GCM)</td>
<td>Zimbabwe</td>
</tr>
<tr>
<td>Folasade Ogunnola</td>
<td>University of Lagos, College of Medicine</td>
<td>Nigeria</td>
</tr>
<tr>
<td>Sean Philpott</td>
<td>Global Campaign for Microbicides (GCM)</td>
<td>United States</td>
</tr>
<tr>
<td>Shira Saperstein</td>
<td>Moriah Fund</td>
<td>United States</td>
</tr>
<tr>
<td>Charles Shagi</td>
<td>London School of Hygiene and Tropical Medicine (LSHTM)/UK National Institute</td>
<td>Tanzania</td>
</tr>
<tr>
<td>Katharine Shapiro</td>
<td>Consultant, Global Campaign for Microbicides (GCM)</td>
<td>India</td>
</tr>
<tr>
<td>Jerome Singh</td>
<td>Centre for the AIDS Programme of Research in South Africa (CAPRISA)</td>
<td>South Africa</td>
</tr>
<tr>
<td>Cathy Slack</td>
<td>HIV/AIDS Vaccines Ethics Group (HAVEG)</td>
<td>South Africa</td>
</tr>
<tr>
<td>Morenike Ukpong</td>
<td>Nigeria HIV Vaccine and Microbicides Advocacy Group</td>
<td>Nigeria</td>
</tr>
<tr>
<td>Lut Van Damme</td>
<td>Contraceptive Research and Development (CONRAD)</td>
<td>United States</td>
</tr>
<tr>
<td>Constancia Watadzaushe</td>
<td>University of Zimbabwe-University of California, San Francisco (UZ-UCSF)</td>
<td>Zimbabwe</td>
</tr>
<tr>
<td>Katie West</td>
<td>Global Campaign for Microbicides (GCM)</td>
<td>United States</td>
</tr>
<tr>
<td>Sydney West</td>
<td>Global Campaign for Microbicides (GCM)</td>
<td>United States</td>
</tr>
<tr>
<td>Study</td>
<td>Study product</td>
<td>Study monitor</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>CONRAD Cellulose Sulfate</td>
<td>Cellulose Sulfate (6% sodium cellulose sulfate)</td>
<td>CONRAD</td>
</tr>
<tr>
<td>FHI Cellulose Sulfate</td>
<td>6% Cellulose Sulfate</td>
<td>FHI</td>
</tr>
<tr>
<td>FHI SAVVY®</td>
<td>1.0% C11G (SAVVY®) vaginal gel</td>
<td>FHI</td>
</tr>
<tr>
<td>HPTN 035</td>
<td>0.5% PRO 2000/5 gel and BufferGel</td>
<td>FHI</td>
</tr>
<tr>
<td>Study</td>
<td>Study product</td>
<td>Study monitor</td>
</tr>
<tr>
<td>---------------</td>
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</tr>
<tr>
<td>MDP 301</td>
<td>0.5% and 2% PBO 2000/5 gel</td>
<td>MDP</td>
</tr>
<tr>
<td>MIRA</td>
<td>Ortho All-Flex Arcing Spring latex diaphragm and Replens lubricant gel</td>
<td>UCSF</td>
</tr>
<tr>
<td>Population Council, Center for Biomedical Research</td>
<td>Carraguard* (PC-515)</td>
<td>Population Council</td>
</tr>
</tbody>
</table>

CONRAID, Contraceptive Research and Development; CS, Cellulose Sulfate; DAIDS, Division of AIDS, US National Institutes of Health; DFID, UK Department for International Development; FHI, Family Health International; HPTN, HIV Prevention Trials Network; HSV-2, herpes simplex virus 2; MDP, Microbicides Development Programme; MIRA, Methods for Improving Reproductive Health in Africa; MRC, UK Medical Research Council; MTN, Microbicide Trials Network; NCHH, National Institute of Child Health and Human Development; NIDA, US National Institute on Drug Abuse; NIH, US National Institutes of Health; NIMH, US National Institute of Mental Health; UCSF, University of California, San Francisco; USAID, US Agency for International Development; WGHI, UCSF Women's Global Health Imperative.

* The study population initially included sexually active women, ages 16 and older and was later changed to women ages 16–40, per a protocol amendment.
### Appendix IV. Comparison of Microbicide Trial Sites Visited as Part of the Standards of Care Mapping Exercise

<table>
<thead>
<tr>
<th>Study site visited</th>
<th>Site description</th>
<th>Demographics and study population</th>
<th>Country HIV prevalence rate</th>
<th>Public health system</th>
<th>Access to HIV care</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTN 035 (PRO 2000 gel and BufferGel) Harare, Zimbabwe</td>
<td>Two study clinics in and around Harare: Spilhaus (periurban) and Seke South (urban). Clinics were stand-alone structures co-located with government health and social service facilities.</td>
<td>Severe economic problems, food and fuel shortages, forced migration, under-nutrition, high unemployment. Women recruited from family planning, STI and postnatal clinics, and community-based locations, or referred from other research projects, health, and social service providers.</td>
<td>20% (UNAIDS/WHO 2007)</td>
<td>Well-developed public infrastructure, health care was fee-for-service. However, suffered from economic and political strife as well as staff shortages, fuel shortages, and drug stockouts. Patients paid for all care unless they received a social welfare exemption (reported to be a somewhat difficult process).</td>
<td>Government clinics close to both sites offered HIV/ART for very low cost, but patients had to first pay for baseline tests, which could be prohibitively expensive. Patients with a CD4 count below 50 were given priority for care.</td>
</tr>
<tr>
<td>MIRA diaphragm study Harare, Zimbabwe</td>
<td>Two study clinics in Harare suburbs of Chitungwiza and Epworth.</td>
<td>Severe economic problems, food and fuel shortages, forced migration, under-nutrition, high unemployment. Women recruited from general health clinics and CBOs, and through advertisements in local media.</td>
<td>20% (UNAIDS/WHO 2007)</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td>Population Council Carraguard® Gugulethu, South Africa</td>
<td>One study clinic, the Empilisweni Centre for Wellness Studies, located in the Ulluntu Community Center in the Cape Town township of Gugulethu.</td>
<td>Periurban township, high unemployment, violent crime, alcohol and drug use. Some squatter camps in the township have no utilities.</td>
<td>21.5% (AIDS 2007)</td>
<td>Free integrated primary health care at public health clinics, including STI, HIV, and TB care, medications, laboratory services, and management of acute and chronic health problems. System was overburdened; too few providers and long waits.</td>
<td>Eight HIV clinics accessible by public transport; ART only offered at one (Crossroads Clinic). At the time of our visit, there was a six-week waiting list for ART unless patient was very ill. Disability grants were available to PLWHA with a CD4 count &lt;200.</td>
</tr>
<tr>
<td>Population Council Carraguard® Soshanguve, South Africa</td>
<td>One study clinic, the Setshaba Research Centre, operating out of a former stand-alone public health clinic.</td>
<td>Periurban township outside of Pretoria, South Africa. High unemployment, violent crime, alcohol and drug use.</td>
<td>21.5% (AIDS 2007)</td>
<td>Same as above</td>
<td>ART initiation and drugs only available at George Mukari Hospital, approximately 18 km from the study clinic. Follow-up care could be accessed at local clinics after initiation. Wait list for treatment.</td>
</tr>
<tr>
<td>MDP 301 (PRO 2000 gel) Africa Centre/Unkhanyakude District, South Africa</td>
<td>Three study clinics (KwaMsane, Mtubatuba, and Madvelani) run out of porta-cabins next door to DoH public health clinics.</td>
<td>Rural and periurban areas. High unemployment, violent crime, out-migration for work. Women recruited from public health clinics. Many women have steady partners but most unmarried.</td>
<td>21.5% (AIDS 2007)</td>
<td>Same as above</td>
<td>Free government programs were available onsite. At the time of our visit, there was no wait for treatment. Initiation of ART occurs at the hospital but follow-up care can be accessed at local clinics. Africa Centre administers local PEPFAR funding.</td>
</tr>
<tr>
<td>Study site visited</td>
<td>Site description</td>
<td>Demographics and study population</td>
<td>Country HIV prevalence rate</td>
<td>Public health system</td>
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</tr>
<tr>
<td>MDP 301 (PRO 2000 gel) Mwanza, Tanzania</td>
<td>Study operates eight mobile clinics set up once weekly in guest houses and hotels close to clusters of participants.</td>
<td>Urban Lake Victoria. Many male partners migrate to and from mines or fishing islands. Study population is highly mobile. Many women are food sellers, local beer sellers, or hotel and restaurant workers. Many engage in transactional sex. It is estimated by study staff that more than half are divorced, widowed, or single.</td>
<td>6.5% (UNAIDS/WHO 2007)</td>
<td>Overburdened public health system. Patients have to pay for all health care except care for children younger than 5 and contraception (although there may be “registration fees” for these services as well).</td>
<td>The ART program in Tanzania was relatively new at the time of our visit. Only a small fraction of those needing treatment were on ART. There was no wait list for treatment. HIV care was available at two government hospitals, and satellite clinics were being trained to provide ART.</td>
</tr>
<tr>
<td>CONRAD Cellulose Sulfate Cotonou, Benin</td>
<td>Main clinic sat in STI reference clinic for the national AIDS control program on the site of a local fee-for-service community hospital.</td>
<td>Urban port city; large transient, migrant population from bordering countries. Study population consisted of women with multiple partners working in hotels.</td>
<td>1.8% (UNAIDS/WHO 2007)</td>
<td>Fee-for-service system, not affordable by many. HIV and STI care are free (TB diagnosis and treatment is fee-for-service). No cervical screening services available.</td>
<td>Main hospital provides ART, and all HIV care is free (funded through GFATM). One of the five sites in the city dispensing ART served as the main study clinic.</td>
</tr>
<tr>
<td>FHI Cellulose Sulfate Nigeria Site not visited</td>
<td>Participants visited main study clinics for screening, enrollment, and follow-up visits. All other study visits held at outreach posts in surrounding community.</td>
<td>Study population consisted of women with multiple partners; many engaged in transactional sex, mostly working out of bars and trailer parks.</td>
<td>5.8% Nigeria (UNAIDS 2002)*</td>
<td>Site not visited</td>
<td>Site not visited</td>
</tr>
<tr>
<td>FHI SAVVY® Ghana and Nigeria Site not visited</td>
<td>Same as above</td>
<td>Study population consisted of young, sexually active women at high risk for acquiring HIV infection.</td>
<td>3% Ghana 5.8% Nigeria (UNAIDS 2002)*</td>
<td>Site not visited</td>
<td>Site not visited</td>
</tr>
</tbody>
</table>


* Figures quoted from the 2002 UNAIDS report, reflecting the estimated national HIV prevalence rates at the time of study design.
Endnotes

2. Global Campaign for Microbicides. Cameroon Tenofovir Trial Case Study. PATH. In press.
23. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended most recently by the 52nd WMA General Assembly, Edinburgh, Scotland, 2000. This is an amendment in the form of a footnote to Paragraph 29, approved by the WMA General Assembly, Washington, DC, 2002.


51. Ibid.


61. Ibid.

62. Ibid.


67. Ibid.


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


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“One of the concerns that communities have been raising [is] that when a trial is coming into their community, they should be benefiting from the trial being there...Completed protocols that have already been signed is what we get. [The researchers] bring [the] finished protocol and say we want to start mobilizing the community now. It’s justified to say that most of the protocols are being imposed on the communities without their...contribution. Ideally it is the grassroots level that should be consulted first and the ones who will be involved. These are issues that we have been raising, that CAB members have been raising.”

—COMMUNITY OUTREACH WORKER