



INTERNATIONAL PARTNERSHIP *for* MICROBICIDES

Guidelines for the Conduct of IPM Clinical Trials

International Partnership for Microbicides
8401 Colesville Road, Suite 200
Silver Spring, MD 20910
United States
www.ipm-microbicides.org

April 2006

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The HIV/AIDS epidemic has its greatest impact in communities where access to health care is limited and social inequity is a significant force in the lives of women and other groups. These conditions create special challenges for ensuring that the rights, autonomy and welfare of clinical trial participants are protected. It is critical that these challenges be openly and effectively addressed. Only by testing microbicides in the countries most profoundly affected by HIV/AIDS can researchers measure the safety, effectiveness and acceptability of these products among the women in most urgent need of new, female-initiated HIV prevention tools.

The International Partnership for Microbicides (IPM) is dedicated to the mission of preventing HIV infection by accelerating the development of microbicides for women in resource-poor countries. We are committed to implementing microbicide clinical trials that meet the highest ethical and regulatory standards, sustain broad community support and leave participating communities better off.

This paper describes guidelines for the conduct of IPM clinical trials. We understand that some aspects of ethical clinical practice resist standardisation across countries and trial sites and will need to be adapted to meet unique local circumstances. We will work closely with local and national governments and development partners so that support for participants and communities involved in clinical trials can be a shared responsibility.

With that in mind, this document defines general principles we will use in implementing clinical research and gives specific details where possible. The paper provides IPM's rationale for particular guidelines and offers relevant context from ethics literature and current ethical practice and discussion. This is meant to be a living document that will be updated as the HIV prevention community learns more about conducting ethically sound and scientifically rigorous microbicide and HIV prevention research in resource-limited settings.

Community Engagement

IPM Guideline: IPM is committed to the participation of local communities prior to, during, and after clinical trials. Each IPM-sponsored trial site will have a community advisory process. In addition, research teams will use individual interviews, community forums and other means to learn about community perspectives and engage community members as partners in research. IPM will also strive to bring local and national stakeholders together, holding joint consultations with government officials, community representatives, people living with and affected by HIV, providers and advocates, to discuss the research and address issues and concerns, including potential stigmatisation of research participants, as they arise. In addition, IPM will regularly provide updates on the status of the clinical trial and will have an end-of-study meeting with communities to present and explain the final results.

Context: The value of community engagement in the design and implementation of clinical research is increasingly recognised among ethicists and trial sponsors. The

closing of two prophylaxis trials in 2005, based largely on community concerns, has dramatised the importance of broad-based community support for trials. Community engagement activities, such as community advisory boards (CABs) and community forums, can also provide researchers with crucial information that facilitates recruitment, retention and community education activities. UNAIDS HIV vaccine research guidelines say that “community representatives should be involved in an early and sustained manner in the design, development, implementation and distribution of results of HIV vaccine research.”¹ Ethical guidance developed by the international HIV Prevention Trials Network (HPTN) notes the creation of a network-wide HPTN Community Working Group, as well as the establishment of a community advisory mechanism at each trial site (usually a CAB). These mechanisms are to provide “advice on scientific and ethical issues regarding study design, recruitment and protection of study volunteers.”² The Global Campaign for Microbicides (GCM) report *Mobilization for Community Involvement in Microbicide Trials*³ defines community involvement in clinical research as a partnership between researchers and communities and it calls for fostering a sense of collaboration and shared ownership between the study team and community members.

Informed Consent

IPM Guideline: Informed consent is the cornerstone of ethical trial conduct. IPM is committed to ensuring that all participants in IPM-sponsored trials have freely given informed consent based on a clear understanding of the study goals and the risks and potential benefits of trial participation. The informed consent process will be consistent with ICH⁴ and local country Good Clinical Practice (GCP) guidelines. Prospective trial participants will be tested for their comprehension of critical concepts discussed in the informed consent process. The process will begin with group counselling sessions, followed by individual meetings. IPM recognises that informed consent is an ongoing process and will ensure continued understanding of trial participation through periodic post enrolment discussions of the risks and benefits of participation with all trial participants. Any participant will be free to withdraw from the trial at any time without affecting their care. In addition, appropriate reimbursement for expenses occurred by trial participants will be determined in consultation with local ethical committees and regulatory agencies.

Context: Ethical guidelines and commentaries developed by the Nuffield Council on Bioethics⁵ note that the importance of receiving informed consent from all research subjects is widely recognised in ethics literature. (The Nuffield documents explore several complex questions involved in informed consent, including the definition of “genuine” consent and the level of information about a trial that must be provided to prospective participants.) A UNAIDS guidance document on clinical trials of HIV

¹ UNAIDS, Ethical considerations in HIV preventive vaccine research, 2000.

² MacQueen, K, Sugarman, J, HIV Prevention Trials Network Ethics Guidance for Research, 15 April 2003, accessed at www.hptn.org/Web%20Documents/EWG/HPTNEthicsGuidanceFINAL15April2003.pdf.

³ Global Campaign for Microbicides, Mobilization for community involvement in microbicide trials: Report from a dialogue in Southern Africa, 2004.

⁴ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

⁵ Nuffield Council on Bioethics, The ethics of research related to health care in developing countries, 2002, and The ethics of research related to health care in developing countries: a follow-up discussion paper, 2005.

vaccines emphasises the ongoing nature of the informed consent process, noting that “efforts should be taken to ensure throughout the trial that participants continue to understand and to participate freely as the trial progresses.”⁶

Risk Reduction Counselling and Provision of Condoms

IPM Guideline: Before and during IPM-sponsored clinical trials, study participants will be required to participate in risk reduction counselling sessions that are consistent with World Health Organization HIV prevention counselling guidelines or national guidelines where appropriate. Risk reduction counselling will be performed at every study visit and will include, among other things, provision and education on the use of male and female condoms. IPM views HIV prevention as a concern of the community as well of the individual, and we will support broader HIV prevention interventions in the communities where research studies are implemented.

Male and female condoms will be provided free of charge to trial participants at every study visit. IPM will either provide contraception counselling and contraceptives, or refer trial participants to appropriate family planning clinics in the community if they want contraception.

Context: Providing quality risk-reduction counselling is an accepted standard in HIV prevention research, as is providing male condoms. Many clinical trials enrolling women do not, however, provide female condoms to participants. IPM has decided to provide female condoms based on studies that suggest they may reduce the risk of HIV and other sexually transmitted infections (STIs).^{7 8} The GCM consensus statement argues that “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.”⁹

Referral for Individuals who Test HIV-Positive at Screening, Prior to Enrolment

IPM Guideline: A comprehensive package of post-test counselling and psychosocial support will be provided to women who test HIV positive during screening and thus are ineligible to participate in the trial. Initial counselling services will be provided at the site and women will be referred to additional counselling, support services and, where available, treatment. These services will be identified by IPM prior to study initiation and referral agreements with local providers will be documented in writing. IPM will strive to establish clinical sites in areas where there is capacity for delivery of antiretroviral (ARV) treatment to the broader community. IPM will work closely with sites and trial participants to facilitate effective referrals.

Context: Standard ethical guidance documents do not stipulate that researchers are obligated to provide services to individuals who are determined to be ineligible for enrolment in a clinical trial. Guaranteeing comprehensive HIV care and treatment to

⁶ UNAIDS, Ethical considerations in HIV preventive vaccine research, 2000.

⁷ Trussell J, Sturgen K, Strickler J, et al. Comparative contraceptive efficacy of the female condom and other barrier methods. *Fam Plann Perspect* 1994;26(2):66-72.

⁸ Further research is needed to more firmly establish the protective efficacy of female condoms.

⁹ Global Campaign for Microbicides, Consensus points on access to treatment and standards of care in HIV microbicide trials, 2005.

all individuals who seek to enrol in a trial would place a heavy burden on trial sponsors. Providing ARVs to individuals ineligible for enrolment may also encourage women with known HIV infection to volunteer for screening so that they can get access to ARVs. In addition, for communities where ARVs are not readily available, there is a legitimate question as to whether it is equitable to provide what amounts to preferential treatment to people who come forward for clinical research. The GCM consensus statement does not argue for an ethical requirement to provide treatment to all those who seek to enrol in trials, but it does suggest that when individuals are referred for services, “researchers and/or trial sponsors should work to ensure that adequate care is actually received through monitoring and support programmes for participants.”¹⁰

STI Screening and Treatment

IPM Guideline: Individuals who are enrolled into IPM-sponsored trials will be offered diagnosis for common STIs during the trial. Trial participants will be offered treatment for curable STIs that are identified. Women with STIs who are not eligible for enrolment will be counselled and referred for treatment in the community. Treatment will be provided at the trial site if local treatment centres cannot be identified.

Context: IPM believes it is morally appropriate and practical to identify curable STIs among study participants and provide care for these conditions. Treatment of STIs in and of itself is an important HIV risk reduction strategy.

Provision of ARVs for Trial Participants

IPM Guideline: Participants in IPM-sponsored trials who become infected with HIV during the course of a trial will be offered appropriate ARV therapy and HIV-related care. The threshold for initiation of ARV treatment will be determined with reference to the host country’s treatment guidelines or, if those guidelines are not in place, through guidelines established by the World Health Organization (WHO). IPM will pay for appropriate ARV treatment until this treatment is available through national HIV treatment programmes or other sources.

In order to ensure sustainable, long-term access to ARVs after clinical trials are complete, IPM will, where possible, establish partnerships with national ministries of health, hospitals, universities or other organisations for care delivery. The process for funding ARV treatment will be handled on a site-to-site basis. IPM plans to establish dedicated financing that can pay for ARVs until national programmes can assume responsibility for providing this care. The chosen financing method will ensure availability of funds independent of IPM’s business and financial status. As countries are developing plans for the scale-up of ARVs, trial participants could be designated as an important group for access to treatment.

Trial participants in IPM-sponsored trials will be tested frequently for HIV during the trial. In the event a participant becomes HIV-infected during a trial, she will immediately be required to stop use of the microbicide under study. In studies of anti-HIV specific drugs, each participant who becomes infected will be offered testing to determine whether the participant’s virus is susceptible to established first-line

¹⁰ Global Campaign for Microbicides, Consensus points on access to treatment and standards of care in HIV microbicide trials, 2005.

therapy. In the event clinically relevant resistance is detected, the participant will have access to ARV treatment licensed in the country appropriate to her infection and related care.

Study participants who seroconvert and become pregnant during the course of a trial will be provided with appropriate Prevention of Mother-to-Child Transmission (PMTCT) services.

Context: At this time, there is no consensus in the ethical literature or standard practice as to whether researchers are obligated to provide ARV therapy to trial participants who become infected with HIV during the course of HIV prevention clinical research.¹¹ There is, however, a steady movement among HIV prevention researchers toward providing this care. A consensus statement developed by the GCM in 2005 calls on the microbicide community to ensure participant access to ARVs “based on ethical aspirations and existing social and political realities.”¹² In 2000, a UNAIDS guidance document on HIV vaccine research said the “ideal (would be) to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country.”¹³ By 2004, an article based on a consultation sponsored by the WHO and UNAIDS stated that “broad agreement now exists among sponsors of HIV prevention trials that antiretroviral therapy (ART) should be provided.”¹⁴

Services for Study Staff

IPM Guideline: IPM study staff who are exposed to potentially infectious materials (hepatitis B virus, hepatitis C virus, or HIV) during study procedures through a percutaneous injury (e.g., a needle stick or cut with a sharp object) or contact with mucous membrane or nonintact skin will be offered the appropriate post-exposure prophylaxis as recommended by the U.S. Centers for Disease Control and Prevention. (ref: MMWR: June 29, 2001/50 (RR11); 1-42) If study staff becomes HIV-infected through trial-related activities, IPM will pay for ARV treatment and HIV-related care until this care and treatment is available through national HIV treatment programmes. IPM will provide all study staff with worker’s compensation coverage. *Context:* IPM considers it a moral obligation to provide our staff with the best available treatment and care for study-related injury.

Treatment and Compensation for Physical Harm

IPM Guideline: If a participant in an IPM-sponsored trial becomes ill or injured as a direct result of participation in the study, medical treatment for the adverse reaction or injury will be provided immediately and free of charge. The study staff will refer the participant for ongoing treatment for the injury, if needed. IPM will pay for appropriate medical expenses for treatment of any such illness or injury.

¹¹ For a thorough discussion of this and other ethical issues involved in clinical research, see *Rethinking the Ethical Roadmap for Clinical Testing of Microbicides* from the Global Campaign for Microbicides, May 2005.

¹² Global Campaign for Microbicides, Consensus points on access to treatment and standards of care in HIV microbicide trials, 2005.

¹³ UNAIDS, Ethical considerations in HIV preventive vaccine research, 2000, Geneva.

¹⁴ WHO/UNAIDS, Treating people with intercurrent infection in HIV prevention trials, *AIDS* 2004, 18:W1-W12.

IPM will pay compensation for illness or injury resulting from the use of products provided in the study, medical treatment for an adverse reaction to those products, or any other procedure that is part of the study.¹⁵ **An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation.**

IPM is also committed to monitoring non-physical or “social harms” such as discrimination or stigma that may arise as a result of an individual’s participation in a trial. IPM staff will make concerted efforts on behalf of trial participants to mitigate the negative effects of these events, should they occur.

Context: The revised Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects* states that investigators have a responsibility to ensure participants have access to free medical treatment and “such financial or other assistance as would compensate them equitably” for injuries.¹⁶ Ethical guidance based on a consultation held by WHO and UNAIDS calls on governments to amend their laws to ensure that trial participants are insured for coverage to address any trial-related harms.¹⁷ The HIV Vaccine Trial Network *Participants’ Bill of Rights and Responsibilities* promises “treatment and payment of resulting medical costs”¹⁸ for physical injuries resulting from trial participation.

Post-Trial Access

IPM Guideline: Ensuring access to microbicides is a responsibility that must be shared by study sponsors, the research team, donors, multilateral and bilateral agencies and, ultimately, national governments. IPM is committed to the principle that all participants in an IPM-sponsored trial will have access to the product studied if the product has been proven to be safe and effective, and has been approved for domestic use in the country. IPM will also make every effort to partner with national governments and other health providers to ensure women in the host community have access to a product that is demonstrated safe and effective in a local trial and licensed for domestic use.

IPM is an advocate for global microbicide access. IPM’s commitment to global access is reflected in several aspects of our work. We seek to identify products for development and testing that are inherently low cost to produce. IPM establishes agreements with commercial partners to ensure our right to make products available in less developed countries. We are committed to expediting regulatory consideration of products demonstrated to be safe and effective. In addition, we are working with donors and international organisations to increase regulatory capacity

¹⁵ Compensation will be paid according to the Clinical Trial Compensation Guidelines developed by the Association of the British Pharmaceutical Industry and adopted by the South African Medicines Control Council. A copy of the guidelines is available from IPM study staff or on the Internet at www.sahealthinfo.org/ethics/book1appen4.htm.

¹⁶ Council for International Organizations of Medical Sciences, *International ethical guidelines for biomedical research involving human subjects*, updated 2002, accessed at: www.cioms.ch.

¹⁷ WHO/UNAIDS, *Treating people with intercurrent infection in HIV prevention trials*, *AIDS* 2004, 18: W1-W12.

¹⁸ HIV Vaccine Trials Network, *Participants’ Bill of Rights and Responsibilities*, accessed at: www.hvtn.org/community/rights.html.

and to establish adequate financing mechanisms to support global microbicide access.

Context: There is no consensus in standard ethical documents about participant access to a product after the trial if the product is licensed for use. The updated Declaration of Helsinki states that “at the conclusion of the study, every patient entered in the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods.”¹⁹ CIOMS argues that researchers may not be able to assure post-trial access to whatever product is being tested, but it advises researchers to “make every effort to ensure any intervention or product developed will be made reasonably available.”^{20 21} The UNAIDS HIV vaccine research guidelines advise that a vaccine proven effective should be made available “to all participants in the trials in which it was tested, as well as to other populations at high risk of HIV infection.”²² The GCM consensus statement argues that trial participants should have preferential access to any test product that is shown effective, and GCM encourages researchers and donors to “actively seek to accelerate access to (the) product post-trial through implementation of observational/introductory studies and negotiation with host country governments and product sponsors.”²³

¹⁹ World Medical Association, The Declaration of Helsinki, updated 2002, accessed at: www.wma.net/e/policy/b3.htm.

²⁰ Council for International Organizations of Medical Sciences, International ethical guidelines for biomedical research involving human subjects, updated 2002, accessed at: www.cioms.ch.

²¹ The Nuffield Council on Bioethics endorsed a U.S. National Bioethics Advisory Commission recommendation that “researchers should endeavour before the initiation of a trial to secure post-trial access for effective interventions for participants in the trial and that the lack of such arrangements should have to be justified to a research ethics committee.”

²² UNAIDS, Ethical considerations in HIV preventive vaccine research, 2000.

²³ Global Campaign for Microbicides, Consensus points on access to treatment and standards of care in HIV microbicide trials, 2005.