INTERNATIONAL PARTNERSHIP *for* MICROBICIDES

Guidelines for Conducting IPM Clinical Trials

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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 prominent in the lives of women and other vulnerable groups. These conditions create special challenges to ensuring that the rights, autonomy and welfare of those volunteers who choose to participate in clinical research are protected. It is critical that these challenges be openly and effectively addressed in the field of HIV prevention research. 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 research on microbicides for women in developing countries. We are committed to implementing microbicide clinical trials that meet international and local ethical and regulatory standards, sustain broad community support and benefit participating communities.

This document describes guidelines for conducting IPM clinical trials of microbicide products particularly in developing countries. Other ethical guidelines apply to IPM's incidence or market research studies. The guidelines are meant to inform the work of IPM and not to supersede policies where IPM research is conducted. We understand that some aspects of ethical clinical practice cannot be standardized across countries and settings and that some policies will need to be adapted to meet distinct 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.

All IPM-sponsored trials are conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki,[1] the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines[2] and country-specific clinical trial guidelines.[3] With that in mind, this document defines general principles we will use in implementing clinical research and gives specific details where possible. The document 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 developing country settings.

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[1] World Medical Association Declaration of Helsinki, *Ethical Principles for Medical Research Involving Human Subjects*, 2008, accessed at: http://www.wma.net/e/policy/b3.htm.

[2] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, *Guideline For Good Clinical Practice E6(R1)*, 1996, accessed at: http://www.ich.org/LOB/media/MEDIA482.pdf.

[3] For example, South Africa Department of Health, *Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa*, 2006, accessed at: http://www.doh.gov.za/docs/factsheets/guidelines/clinical-f.html.

Community Engagement

IPM Guideline: IPM is committed to the participation of local communities prior to, during and after clinical trials. Each IPM-supported clinical research centre will have a community advisory process and a community engagement plan. 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 at various points in the clinical trial process. As a general rule, community representatives are provided an opportunity to comment on study protocols in advance of finalization; this process is coordinated by the local research centres.

IPM will strive to bring local and national stakeholders together, holding 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 as they arise. In addition, the research centres will regularly provide updates on the status of the clinical trial, and will share final study results with the communities hosting the trials and the local ethics committees. IPM, in collaboration with the research centres, will also provide study results to national regulatory agencies, government representatives and other stakeholders as appropriate.

Non-physical or social harms (such as discrimination or stigma that may arise as a result of an individual's participation in a trial) will be monitored by the research centres, and participants will be referred to social services, as appropriate. IPM will make concerted efforts to build community support for the trial and trial participants, and to minimize social harms.

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 pre-exposure prophylaxis trials in 2005, based largely on community concerns, highlighted the importance of broad-based community support for trials. Community engagement mechanisms, such as community advisory boards (CABs) and community forums, can also provide researchers with crucial information that facilitates participant recruitment, retention and community education activities. In addition, these mechanisms provide "advice on scientific and ethical issues regarding study design, recruitment and protection of study volunteers."[4]

The Joint United Nations Program on HIV/AIDS (UNAIDS)/World Health Organization (WHO) ethical guidelines for HIV prevention trials, published in 2007, call on researchers and trial sponsors to "consult communities through a transparent and meaningful participatory process which involves them in an early and sustained manner in the design, development, implementation, monitoring, and distribution of results of biomedical HIV prevention trials."[5] The UNAIDS/AIDS Vaccine Advocacy Coalition (AVAC) guidelines on good participatory practices, also published in 2007, state that "outreach and education efforts are key to build capacity and contribute to the empowerment of these communities as decision-making agents and advocates in

[4] HIV Prevention Trials Network (HPTN) Ethics Working Group, *Ethics Guidance for Research*, 2003, accessed at: www.hptn.org/Web%20Documents/EWG/HPTNEthicsGuidanceFINAL15April2003.pdf.

[5] UNAIDS/WHO, *Ethical Considerations in Biomedical HIV Prevention Trials*, 2007, accessed at: http://data.unaids.org/pub/Report/2007/jc1399-ethicalconsiderations_en.pdf.

the research process." Relevant activities mentioned include "formative research, communications and education plans, and establishment of community advisory mechanisms" as well as monitoring and evaluation plans.[6]

Informed Consent Process

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 trial, including the potential risks and benefits of trial participation.

The informed consent process will be consistent with ICH GCP and local country guidelines, and will be performed at both screening and enrolment in trials. The process will include one-on-one meetings with volunteers, and may be preceded by group orientation sessions. IPM recognises that informed consent is an ongoing process that requires periodic discussions with participants to ensure their continued understanding of the trial and their consent to be involved. Participants are free to withdraw from the trial at any time and for any reason.

Appropriate reimbursement for expenses incurred by trial participants will be determined in consultation with local ethics committees and regulatory agencies.

Context: The central importance of receiving informed consent from all participants in medical research is widely recognised in ethics literature. The Nuffield Council on Bioethics discussion papers[7] 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. UNAIDS/WHO ethical considerations for HIV prevention trials note that "researchers and research staff should take efforts to ensure throughout the trial that participants continue to understand and to participate freely as the trial progresses" and that "participants should also receive reimbursement for travel and other expenses."[8]

Risk Reduction Counselling and Provision of Condoms

IPM Guideline: During screening and after enrolment in IPM clinical trials, participants will be required to participate in risk reduction counselling sessions that are consistent with World Health Organization HIV and STI prevention counselling guidelines, or national guidelines where appropriate. Risk reduction counselling will be performed at every trial visit and will include, among others, provision and education on the use of male condoms, as well as female condoms depending on the trial design.

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[6] UNAIDS/AIDS Vaccine Advocacy Coalition, *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*, 2007, accessed at: http://data.unaids.org/pub/Manual/2007/jc1364_good_participatory_guidelines_en.pdf.

[7] Nuffield Council on Bioethics, *The Ethics of Research Related to Health Care in Developing Countries*, 2002, and *Follow-up Discussion Paper*, 2005, accessed at: http://www.nuffieldbioethics.org/go/publications/latest_30.html.

[8] UNAIDS/WHO, *Ethical Considerations in Biomedical HIV Prevention Trials*, 2007, accessed at: http://data.unaids.org/pub/Report/2007/jc1399-ethicalconsiderations_en.pdf.

New HIV risk-reduction methods will be added, if appropriate, as they are scientifically validated and approved for use by relevant international and national authorities.

Context: Providing quality risk-reduction counselling is an accepted standard in HIV prevention research, as is providing condoms. According to UNAIDS and WHO, "appropriate counselling and access to all state of the art HIV risk-reduction methods" should be provided to trial participants.[9]

STI Screening and Treatment

IPM Guideline: Participants in IPM clinical trials will be assessed for common sexually transmitted infections (STIs) and will be offered or referred for treatment for curable STIs that are identified. Participants will be encouraged to notify their partners to seek testing and treatment as well.

Women who have STIs that result in ineligibility for enrolment will be counselled and referred for treatment and care with a referral letter. Research centres will ensure that STI treatment is available in the community prior to trial initiation.

Context: IPM believes it is morally appropriate to identify sexually transmitted infections among trial participants and to provide care for these conditions as appropriate. Treatment of STIs in and of itself is an important HIV risk-reduction strategy. [10]

Contraception and Management of Pregnancy

IPM Guideline: In the interests of safety, all participants in IPM clinical trials must be on a stable form of contraception at the time of enrolment and for the duration of their participation in the clinical trial. A stable form of contraception does not entail the sole use of condoms, but refers primarily to the use of reliable contraceptive hormones or devices (such as intrauterine devices).

Participation in trials is voluntary and contraceptive use will be discussed during the informed consent process. Participants will have the option of obtaining contraception from a family planning facility or from the research centre for the duration of the clinical trial. They will also receive ongoing contraceptive counselling throughout the trial.

Participants who nevertheless become pregnant will discontinue use of the investigational product and will be referred to the appropriate clinic for further management of the pregnancy. Data will be collected documenting the progress and outcome of pregnancy and the first year of life of the infant, if applicable.

Context: In several microbicide efficacy trials, a relatively high rate of pregnancies has occurred. In the interest of safety, IPM feels it is appropriate to do all that is reasonably possible to prevent trial participants from becoming pregnant while using an investigational product.

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[9] UNAIDS/WHO, *Ethical Considerations in Biomedical HIV Prevention Trials*, 2007, accessed at: http://data.unaids.org/pub/Report/2007/jc1399-ethicalconsiderations_en.pdf.

[10] Ibid.

In addition, according to a GCM consensus statement, "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."[11] The UNAIDS/WHO ethical guidelines also note that "appropriate reproductive and sexual health counselling and ancillary services, including family planning, should be provided to trial participants," and that researchers "should maintain pregnancy registries to collect data on the outcomes of pregnancy" and "follow up babies born to women participants."[12]

Referral for Volunteers Who Test HIV-Positive at Screening

IPM Guideline: Pre- and post-test counselling 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 post-HIV testing at the clinical research centre, and women will be referred to additional counselling, support and treatment services. These services will be identified prior to trial initiation, and referral systems with local providers will be arranged in advance by the research centre.

IPM will strive to establish clinical research centres in areas where there is capacity for HIV-related care and delivery of antiretroviral (ARV) treatment to the broader community. IPM will work closely with research centres 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 all those who seek to enrol in a trial would place a heavy burden on trial sponsors, and may encourage people with known HIV infection to volunteer for screening so that they can gain access to ARVs. In addition, for communities in which 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."[13]

Provision of ARV Treatment for Clinical Trial Participants

IPM Guideline: Participants in IPM clinical trials will be tested frequently for HIV during the trial, and risk reduction counselling will be performed at every visit. If some participants become infected with HIV during the trial, they will be referred for

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[11] Global Campaign for Microbicides, *Consensus Points on Access to Treatment and Standards of Care in Microbicide Trials*, 2005, accessed at: http://www.global-campaign.org/clientfiles/Statement_of_Care_Nov%208.pdf.

[12] UNAIDS/WHO, *Ethical Considerations in Biomedical HIV Prevention Trials*, 2007, accessed at: http://data.unaids.org/pub/Report/2007/jc1399-ethicalconsiderations_en.pdf.

[13] Global Campaign for Microbicides, *Consensus Points on Access to Treatment and Standards of Care in Microbicide Trials*, 2005, accessed at: http://www.global-campaign.org/clientfiles/Statement_of_Care_Nov%208.pdf.

appropriate HIV-related care and ARV treatment. The threshold for initiation of ARV therapy 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).[14,15]

As mentioned above, IPM-supported research centres are typically established in areas where there is capacity for HIV-related care and delivery of ARV treatment. In order to ensure sustainable long-term access to ARV treatment after clinical trials have been completed, partnerships will be established, where possible, with national ministries of health, hospitals, universities or other organisations for treatment and care delivery. IPM plans to establish dedicated financing that can pay for ARVs in the event that national programmes are unable to assume ongoing responsibility for providing this care. IPM-supported care will be provided at health centres in the community, not at the research centres. The chosen financing method will ensure availability of funds independent of IPM's business and financial status.

Participants who become infected with HIV during the course of a trial will immediately be required to stop use of the microbicide product, and will be offered testing to determine whether the virus is susceptible to established first-line therapy. If cases of clinically relevant resistance are detected, participants will have access to ARV treatment and related care that is licensed in their country and appropriate to their infection as soon as they become eligible for treatment.

The possibility of developing ARV drug resistance following use of an ARV-based microbicide can best be addressed during and after an efficacy trial. Participants who acquire HIV during an IPM safety or efficacy trial will be encouraged to enrol in a follow-up study to evaluate the drug resistance profile in HIV-positive women who had been using an ARV-based microbicide or placebo at the time of infection.

Participants who seroconvert and become pregnant during the course of an IPM trial will be referred for appropriate Prevention-of-Mother-to-Child Transmission (PMTCT) services in accordance with host country guidelines, or if these guidelines are not in place, in accordance with guidelines established by WHO.

Context: 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."[16] Consensus on the level of care and treatment has emerged in recent years; the 2007 UNAIDS/WHO ethical guidelines state that "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 recognised as optimal" and that trials "should

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[14] World Health Organization, *Scaling up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach*, 2003, accessed at: http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf.

[15] World Health Organization, *Prioritizing Second-line Antiretroviral Drugs for Adults and Adolescents: A Public Health Approach*, 2007, accessed at: http://www.who.int/hiv/pub/meetingreports/second_line_art_report_2008.pdf.

[16] Global Campaign for Microbicides, *Consensus Points on Access to Treatment and Standards of Care in Microbicide Trials*, 2005, accessed at: http://www.global-campaign.org/clientfiles/Statement_of_Care_Nov%208.pdf.

undertake to support such therapy until individuals become eligible for the national program of care and treatment in their country."[17]

UNAIDS and WHO also recommend that countries include HIV prevention trial participants in their priority list for access to treatment, as national plans for ARV scale-up are implemented.[18]

Treatment and Compensation for Physical Harm

IPM Guideline: If a participant in an IPM clinical trial becomes ill or injured as a result of participation in the trial, medical treatment for the adverse reaction or injury will be provided as appropriate. The research centre 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.

IPM will pay compensation for illness or injury resulting from the use of products provided in the trial along with medical treatment for an adverse reaction to those products, or any other procedure that is part of the trial.[19]

Note: An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation. Please refer to the section on "Provision of ARV Treatment for Clinical Trial Participants" for this information.

Context: The revised Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Biomedical Research* 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.[20] 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.[21]

Services for Research Centre Staff

IPM Guideline: IPM-supported research centre staff who are exposed to potentially infectious materials during trial procedures through a percutaneous injury (a needle stick or cut with a sharp object) or contact with mucous membrane or non-intact skin

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[17] UNAIDS/WHO, *Ethical Considerations in Biomedical HIV Prevention Trials*, 2007, accessed at: http://data.unaids.org/pub/Report/2007/jc1399-ethicalconsiderations_en.pdf.

[18] UNAIDS/WHO, *Ethical Considerations in Biomedical HIV Prevention Trials*, 2007, accessed at: http://data.unaids.org/pub/Report/2007/jc1399-ethicalconsiderations_en.pdf.

[19] 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, available at: www.sahealthinfo.org/ethics/book1appen4.htm.

[20] Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, 2002, accessed at: http://www.cioms.ch/frame_guidelines_nov_2002.htm.

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

will be offered post-exposure prophylaxis as recommended by local or international guidelines, as appropriate.[22,23]

If a research centre staff member becomes HIV-positive through trial-related activities, IPM will pay for HIV-related care and ARV treatment in the event that appropriate care and treatment is not available through national programmes.

IPM ensures that research centres are able to provide psychosocial support, including counselling, as requested and required by the study staff.

Context: IPM considers it a moral obligation to provide research centre staff with the best available treatment and care for trial-related injury. In addition, provision of psychosocial services aids recruitment and retention of high quality staff.

Post-Trial Access to Microbicide Products

IPM Guideline: Ensuring access to microbicides is a responsibility that must be shared by trial sponsors, the research teams, 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 where a clinical trial is held. 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 many aspects of our work. We seek to identify quality products for development and testing that are inherently low-cost to produce. We establish agreements with partners to ensure our right to make products available in developing countries. We are committed to expediting regulatory approval of products demonstrated to be safe and effective. We are working with donors and international organisations to increase regulatory capacity and to establish adequate financing mechanisms to support global microbicide access.

Context: 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."[24] CIOMS argues that researchers may not be able to ensure 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."[25]

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[22] WHO/ILO, *Joint Guidelines on Post-Exposure Prophylaxis (PEP) to Prevent HIV Infection*, 2008, accessed at: http://www.who.int/hiv/pub/guidelines/PEP/en/index.html.

[23] CDC, *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV and HIV and Recommendations for Postexposure Prophylaxis*, MMWR 2005;54 (RR-09):1-17, http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5409a1.htm and MMWR 2001;50 (RR-11):1-42, http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5011a1.htm.

[24] World Medical Association, Declaration of Helsinki, *Ethical Principles for Medical Research Involving Human Subjects*, 2008, accessed at: http://www.wma.net/e/policy/b3.htm.

[25] Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, 2002, accessed at: http://www.cioms.ch/frame_guidelines_nov_2002.htm.

The UNAIDS/WHO ethical guidance document advises that "once a trial product has proven safe and effective, sponsors and researchers should work with development partners, national governments, local authorities and industry where relevant, to ensure planning for its manufacturing, regulatory approval, fair distribution, and efficient delivery in the community engaged in the trial and the country."[26]

[26] UNAIDS/WHO, *Ethical Considerations in Biomedical HIV Prevention Trials*, 2007, accessed at: http://data.unaids.org/pub/Report/2007/jc1399-ethicalconsiderations_en.pdf.