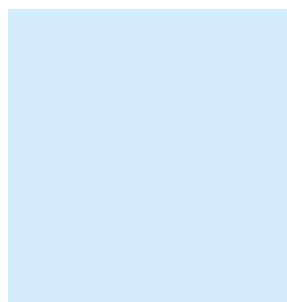


Ethical considerations in biomedical HIV prevention trials

[Additional guidance point added in 2012]

UNAIDS/WHO guidance document



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Catherine Hankins, Carmel Shalev and Jolene Nakao finalized revisions after the Montreux meeting. Mihika Acharya and Constance Kponvi assisted with editing and Lon Rahn did the layout.

A companion document which readers may wish to consult is the UNAIDS/AVAC *Good Participatory Practice for Biomedical HIV Prevention Trials*. It covers core principles and essential activities throughout the research life-cycle, providing a foundation for community engagement in research. It is available on the UNAIDS website in a number of languages. For more information please contact gpp@unaids.org.

Comments on the *Ethical considerations in biomedical HIV prevention trials* and experience with implementation of this guidance are welcome. Please send them to ethics@unaids.org

In 2010-11, UNAIDS and WHO convened three key stakeholder consultations in Istanbul, Kuala Lumpur, and Buenos Aires for the Eastern Europe/Central Asia, Asia, and Americas regions where injecting drugs with contaminated equipment is an important HIV transmission mode. Recommendations from these consultations informed the development of guidance point 20 addressing the meaningful engagement in biomedical HIV prevention trials of people who inject drugs.

* Those who did not attend the Montreux meeting

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Guidance Point 1: Development of Biomedical HIV Prevention Interventions

Given the human, public health, social, and economic severity of the HIV epidemic, countries, development partners, and relevant international organisations should promote the establishment and strengthening of sufficient capacity and incentives to foster the early and ethical development of additional safe and effective biomedical HIV prevention methods, both from the point of view of countries and communities in which biomedical HIV prevention trials take place, and from the point of view of trial sponsors and researchers.

Guidance Point 2: Community Participation

To ensure the ethical and scientific quality and outcome of proposed research, its relevance to the affected community, and its acceptance by the affected community, researchers and trial sponsors should 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.

Guidance Point 3: Capacity Building

Development partners and relevant international organisations should collaborate with and support countries in strategies to enhance capacity so that countries and communities in which trials are being considered can practice meaningful self-determination in decisions about the scientific and ethical conduct of biomedical HIV prevention trials and can function as equal partners with trial sponsors, local and external researchers, and others in a collaborative process.

Guidance Point 4: Scientific and Ethical Review

Researchers and trial sponsors should carry out biomedical HIV prevention trials only in countries and communities that have appropriate capacity to conduct independent and competent scientific and ethical review.

Guidance Point 5: Clinical Trial Phases

As phases I, II, and III in the clinical development of a biomedical HIV preventive intervention all have their own particular scientific requirements and specific ethical challenges, researchers and trial sponsors should justify in advance the choice of study populations for each trial phase, in scientific and ethical terms in all cases, regardless of where the study population is found. Generally, early clinical phases of biomedical HIV prevention research should be conducted in communities that are less vulnerable to harm or exploitation, usually within the sponsor country. However, countries may choose, for valid

scientific and public health reasons, to conduct any trial phase within their populations, if they are able to ensure sufficient scientific infrastructure and sufficient ethical safeguards.

Guidance Point 6: Research Protocols and Study Populations

In order to conduct biomedical HIV prevention trials in an ethically acceptable manner, researchers and relevant oversight entities should ensure that the research protocol is scientifically appropriate and that the interventions used in the experimental and control arms are ethically justifiable.

Guidance Point 7: Recruitment of Participants.

In order to conduct biomedical HIV prevention trials in an ethically acceptable manner, participation of individuals should be voluntary and the selection of participating communities and individuals must be fair and justified in terms of the scientific goals of the research.

Guidance Point 8: Vulnerable Populations

The research protocol should describe the social contexts of a proposed research population (country or community) that create conditions for possible exploitation or increased vulnerability among potential trial participants, as well as the steps that will be taken to overcome these and protect the rights, the dignity, the safety, and the welfare of the participants.

Guidance Point 9: Women

Researchers and trial sponsors should recruit women into clinical trials in order to verify safety and efficacy from their standpoint, including immunogenicity in the case of vaccine trials, since women throughout the life span, including those who may become pregnant, be pregnant or be breastfeeding, should be recipients of future safe and effective biomedical HIV prevention interventions. During such research, women should receive adequate information to make informed choices about risks to themselves, as well as to their foetus or breastfed infant, where applicable.

Guidance Point 10: Children and Adolescents

Children and adolescents should be included in clinical trials in order to verify safety and efficacy from their standpoint, in addition to immunogenicity in the case of vaccines, since they should be recipients of future biomedical HIV preventive interventions. Researchers, trial sponsors, and countries should make efforts to design and implement biomedical HIV prevention product development programmes that address the particular safety, ethical, and legal considerations relevant for children and adolescents, and safeguard their rights and welfare during participation.

Guidance Point 11: Potential Harms

Research protocols should specify, as fully as reasonably possible, the nature, magnitude, and probability of all potential harms resulting from participation in a biomedical HIV prevention trial, as well as the modalities by which to minimise the harms and mitigate or remedy them.

Guidance Point 12: Benefits

The research protocol should provide an accurate statement of the anticipated benefit of the procedures and interventions required for the scientific conduct of the trial. In addition, the protocol should outline any services, products, and other ancillary interventions provided in the course of the research that are likely to be beneficial to persons participating in the trials.

Guidance Point 13: Standard of Prevention

Researchers, research staff, and trial sponsors should ensure, as an integral component of the research protocol, that appropriate counselling and access to all state of the art HIV risk reduction methods are provided to participants throughout the duration of the biomedical HIV prevention trial. New HIV-risk-reduction methods should be added, based on consultation among all research stakeholders including the community, as they are scientifically validated or as they are approved by relevant authorities.

Guidance Point 14: Care and Treatment

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. 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.

Guidance Point 15: Control Groups

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.

Guidance Point 16: Informed Consent

Each volunteer being screened for eligibility for participation in a biomedical HIV prevention trial should provide voluntary informed consent based on complete, accurate, and appropriately conveyed and understood information

before s/he is actually enrolled in the trial. 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. Informed consent, with pre- and post-test counselling, should also be obtained for any testing for HIV status conducted before, during, and after the trial.

Guidance Point 17: Monitoring Informed Consent and Interventions

Before a trial commences, researchers, trial sponsors, countries, and communities should agree on a plan for monitoring the initial and continuing adequacy of the informed consent process and risk-reduction interventions, including counselling and access to proven HIV risk-reduction methods.

Guidance Point 18: Confidentiality

Researchers and research staff must ensure full respect for the entitlement of potential and enrolled participants to confidentiality of information disclosed or discovered in the recruitment and informed consent processes, and during conduct of the trial. Researchers have an ongoing obligation to participants to develop and implement procedures to maintain the confidentiality and security of information collected.

Guidance Point 19: Availability of Outcomes

During the initial stages of development of a biomedical HIV prevention trial, trial sponsors and countries should agree on responsibilities and plans to make available as soon as possible any biomedical HIV preventive intervention demonstrated to be safe and effective, along with other knowledge and benefits helping to strengthen HIV prevention, to all participants in the trials in which it was tested, as well as to other populations at higher risk of HIV exposure in the country, potentially by transfer of technology.

Guidance Point 20: People Who Inject Drugs

Researchers and sponsors should include people who inject drugs in biomedical HIV prevention trials in order to verify safety, efficacy, and effectiveness from their standpoint, including immunogenicity in the case of vaccines. As with other key populations at higher risk of HIV exposure, providing people who inject drugs with access to proven, effective HIV preventive interventions is a public health imperative. Researchers and trial sponsors should engage meaningfully with people who inject drugs and with other stakeholders to overcome the complex legal, ethical, and regulatory challenges to the participation in biomedical HIV prevention trials of people who inject drugs. Trial conduct that is ethical is informed by the latest scientific evidence on proven HIV prevention strategies and ensures that participants' human rights, safety, and welfare are protected.

INTRODUCTION

Well into the third decade of the HIV pandemic, there remains no effective HIV preventive vaccine, microbicide, product or drug to reduce the risk of HIV acquisition. As the numbers of those infected by HIV and dying from AIDS continue to increase, the need for such biomedical HIV preventive interventions becomes ever more urgent. Several such products are at various stages of development, including some currently in phase III efficacy trials. The successful development of effective HIV preventive interventions requires that many different candidates be studied simultaneously in different populations around the world. This in turn will require a large international cooperative effort drawing on partners from various health sectors, inter-governmental organisations, government, research institutions, industry, and affected populations. It will also require that these partners be able and willing to address the difficult ethical concerns that arise during the development of biomedical HIV prevention products.

Following deliberations during 1997–99 involving lawyers, activists, social scientists, ethicists, vaccine scientists, epidemiologists, non-governmental organisation (NGO) representatives, people living with HIV, and people working in health policy from a total of 33 countries, UNAIDS published a guidance document on ethical considerations in HIV preventive vaccine research in 2000. Since then there have been numerous developments related to the conduct of biomedical HIV prevention trials, including vaccine trials. Consultations have been held to explore key issues such as:

- Creating effective partnerships, collaboration and community participation in HIV prevention trials (International AIDS Society (IAS) 2005; UNAIDS 2006; UNAIDS/AIDS Vaccine Advocacy Coalition (AVAC) 2007);

- The inclusion of adolescents in HIV vaccine trials (WHO/IVR 2002; WHO/UNAIDS 2004; WHO/UNAIDS/African AIDS Vaccine Program 2006);
- Gender considerations related to enrolment and informed consent (WHO/UNAIDS 2004);
- Provision of support, care and treatment to participants and the community engaged in HIV prevention trials (WHO/UNAIDS 2003; IAS 2005; UNAIDS 2006; Forum for Collaborative Research 2006; International AIDS Society Industry Liaison Forum 2007);
- Post-trial responsibilities of sponsors, researchers and local providers (AVAC and the International Council of AIDS Service Organizations, 2005).

In light of these consultations, and evolution in the level of prevention, treatment and care available in the era of ‘Towards Universal Access’, the 2000 guidance document was revised and updated. The revision incorporates developments which have taken place since the original publication, including lessons learned in the field of biomedical HIV prevention research. Many different strategies for HIV prevention are now being explored, including microbicides, vaccines, female-initiated barrier methods, herpes simplex virus-2 (HSV-2) treatment/suppression, index partner treatment, antiretroviral pre-exposure prophylaxis, prevention of mother-to-child transmission and drug substitution/maintenance for injecting drug users. Of note, following the compelling evidence of a 50 to 60 per cent reduction in HIV acquisition for men who became circumcised in three randomised controlled trials in South Africa, Kenya and Uganda, WHO/UNAIDS produced recommendations in 2007 judging adult male circumcision to be an accepted risk reduction measure in men, particularly in high prevalence generalised HIV epidemics in which heterosexual transmission predominates. Finally, the guidelines in this document specifically address trials of biomedical HIV preventive interventions but are relevant to those engaged in trials of various behavioural HIV prevention methods.

This document does not purport to capture the extensive discussion, debate, consensus, and disagreement which have taken place among stakeholders in HIV prevention research. Rather it highlights, from the perspective of UNAIDS and WHO, some of the critical ethical elements that must be considered during the development of safe and effective biomedical HIV prevention interventions. Where these are adequately addressed, in the view of UNAIDS/WHO, by other existing texts, there is no attempt to duplicate or replace these texts, which should be consulted extensively throughout biomedical HIV prevention product development activities. Such texts include: the *Nuremberg Code* (1947); the *Declaration of Helsinki*, first adopted by the World Medical Association in 1964 and most recently amended in 2000; the revised *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, issued in 2002 by the Council for International Organisations of Medical Sciences (CIOMS) (and developed in close cooperation with WHO); the World Health Organization's *Handbook for Good Clinical Research Practice* (2005); the *International Conference on Harmonisation's Good Clinical Practice (ICH GCP) Guideline* (1996); and the UNAIDS *Interim Guidelines on Protecting the Confidentiality and Security of HIV Information* (2007).

Systematic guidance on the role and responsibilities of entities funding and conducting biomedical HIV prevention trials towards participants, and their communities can be found in the UNAIDS/AVAC *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials* (2007).

It is hoped that this document will be of use to potential research volunteers and trial participants, investigators, research staff, community members, government representatives, pharmaceutical companies and other industry partners and trial sponsors, and ethical and scientific review committees involved in the development of biomedical HIV prevention products and interventions. It suggests standards, as well as processes for arriving at standards which can be used as a frame of reference from which to conduct further discussion at the local, national, and international levels and can inform the development of national guidelines for the conduct of biomedical HIV prevention trials.

CONTEXT

The HIV pandemic is characterised by unique biological, social and geographical factors that, among other things, affect the balance of risks and benefits for individuals and communities who participate in biomedical HIV prevention trials. These factors may require that additional efforts be taken to address the needs of participating individuals and communities. They have an urgent need for additional HIV prevention choices for use at various stages of the life-cycle, a need to have their rights protected and their welfare promoted in the context of the development and testing of novel HIV prevention modalities, and a need to be able to participate fully as equal participants in the research process. These factors include the following:

- The global burden of disease and death related to HIV continues to increase at a rate unmatched by any other pathogen. For many countries, AIDS is the leading cause of death. Currently available treatments do not lead to cure, but do slow the progression of disease. The most effective treatment for slowing HIV-related disease progression, antiretroviral medication, is a life-long treatment which requires close medical monitoring, is still very costly, especially for 2nd line regimens, and can cause significant adverse effects. Because of this, antiretroviral medication is not readily available to the vast majority of people living with HIV who need it. More than 2 million people had access to antiretroviral treatments in low- and middle-income countries in 2006, five times more people than in 2003. But despite this tremendous progress in the roll-out of antiretroviral treatment, global coverage of needs is below 30%.
- For every person placed on antiretroviral treatment in 2006, another six people became newly infected with HIV. There is therefore an ethical imperative to seek, as urgently as possible, effective and accessible biomedical HIV prevention technologies, to complement existing prevention strategies. This ethical

imperative demands that these technologies be developed to address the situation of those people and populations most vulnerable to exposure to HIV infection.

- Genetically distinct subtypes of HIV have been described, and different HIV subtypes are predominant in different regions and countries. The relevance of these sub-types to probabilities of HIV transmission and acquisition, speed of disease progression and potential protection is not clearly understood.
- For the conduct of efficacy trials of any biomedical HIV prevention product, the populations with the highest incidence of HIV will be those most likely to be considered for participation and would be those most likely to benefit from an effective intervention. However, for a variety of reasons, these populations may be relatively vulnerable to exploitation and harm in the context of biomedical HIV prevention trials. Trial sponsors, countries, researchers, research staff and community leaders must make additional efforts to overcome this vulnerability.
- In some biomedical HIV prevention trials, individuals other than the trial participants may experience risks if they are exposed to the experimental product and may experience benefits if the product is effective. For example in trials of prophylaxis of mother-to-child transmission, the foetus is exposed to the prophylactic antiretroviral regimen in addition to the mother. If the mother develops antiretroviral resistance, she may transmit resistant virus to the infant. When the intervention is effective, the newborn baby is protected. In trials of vaginal microbicides, male sexual partners may be exposed to the product even when condoms are used. In trials of successful vaccine candidates, not only sexual partners benefit but communities may benefit from population level effects.
- Some biomedical HIV prevention modalities may be conceived and manufactured in laboratories of one country (sponsor country or countries), usually in high-income countries, and tested in human populations in another country, often low- and middle-income countries. The potential imbalance of such a

situation demands particular attention to ways to address the differing perspectives, interests and capacities of trial sponsors, countries, and communities engaged in trials with the goal of encouraging the urgent development of additional safe and effective biomedical HIV prevention tools, in ethically acceptable manners, and their early distribution to populations most in need. Countries and communities considering participation in biomedical HIV prevention trials should be encouraged and given the capacity to make decisions for themselves regarding their participation, based on their own health and human development priorities, in a context of equal collaboration with sponsors.

- HIV infection is both highly feared and stigmatised. This is in large part because it is associated with blood, death, sex, and activities which may not be legally sanctioned, such as commercial sex, men having sex with men, and illicit substance use. These are issues which are often difficult to address openly – at a societal and individual level. As a result, people living with HIV and those affected by AIDS may experience stigma, discrimination, and even violence; some communities continue to deny the existence and prevalence of HIV infection. Furthermore, vulnerability to HIV exposure and to the impact of AIDS is greater where people are marginalized due to their social, economic, and legal status. These factors increase the risk of social and psychological harm for people participating in biomedical HIV prevention trials. Additional efforts must be made to address these increased risks and to ensure that the risks participants take are justified by the anticipated benefits of the preventive intervention to the participants themselves or to others in the future.
- A key means by which to protect participants and the communities from which they come is to ensure that the community in which the research is carried out is meaningfully involved in the design, implementation, monitoring, and dissemination of results of HIV prevention trials, including the involvement of representatives from marginalized communities from which participants are drawn.

- Site selection for moving forward into empirical efficacy trials of biomedical HIV prevention technologies is a major challenge. Part of this challenge is the need to integrate biomedical HIV prevention tool development with other HIV prevention modalities, all of which need to be integrated with HIV treatment and care as provided by the local health care system. It is imperative that appropriate financial arrangements are in place to implement agreements made between partners at the time a study is initiated. These agreements should cover the period of the trial but also address what will be provided to study participants once the study is completed. Advance planning and collaboration between partners is also needed to facilitate timely product licensure and distribution once a method has been proven safe and effective.
- It has been the experience to date that HIV incidence in both the experimental and control arms of biomedical HIV prevention trials tends to fall below the pre-trial incidence, presumably as a result of sustained risk-reduction counselling and provision of effective HIV prevention tools. The discovery of additional safe and effective biomedical HIV preventive interventions will necessitate discussions among all research stakeholders involved in planned or active trials of other biomedical HIV prevention tools. A decision to introduce the new method in a trial that is already underway has to be made collectively as it may have implications for resource requirements, sample sizes, and potential futility of continuing the trial. The possibility that such a decision could be required should be anticipated during initial discussions among the research stakeholders.
- No single biomedical HIV prevention product or intervention is now or will be 100 per cent effective. This is in part because none are expected to achieve 100 per cent efficacy in the controlled circumstances of a trial and in part because behaviour will influence both consistency and correctness of uptake for many of the interventions being investigated, with the result that the efficacy seen in the trial will not lead to effectiveness at the same level in the real world. Furthermore, the manner in which an effective biomedical HIV prevention product is introduced into comprehensive HIV prevention programming will affect the

extent to which risk compensation¹ will occur. Therefore, social change communication strategies which emphasize combination prevention will be crucial to ensure that a new biomedical HIV prevention product truly does add to the existing tools when it is introduced.²

Selected circumstances in which biomedical HIV prevention trials should not be conducted

- ✘ when the product to be tested would not be appropriate for use, should it be proven safe and effective, in the community that would participate in the trial (see **Guidance Point 1**);
- ✘ when capacity to conduct independent and competent scientific and ethical review does not exist (see **Guidance Point 4**);
- ✘ where truly voluntary participation and ongoing free informed consent cannot be obtained (see **Guidance Point 7**);
- ✘ when conditions affecting potential vulnerability or exploitation may be so severe that the risk outweighs the benefit of conducting the trial in that population (see **Guidance Point 8**);
- ✘ when a survey of protective local laws and regulations applicable at the trial site has not been conducted or when such a survey indicates insurmountable legal barriers (see **Guidance Point 10**);
- ✘ when agreements have not been reached among all research stakeholders on standard of prevention (see **Guidance Point 13**) and access to care and treatment (see **Guidance Point 14**);
- ✘ when agreements have not been arrived at on responsibilities and plans to make a trial product which proves safe and effective affordably available to communities and countries where it has been tested (see **Guidance Point 19**).

¹ Risk compensation: an increase in risk-taking as a result of a decrease in perception of risk.

² The term “combination prevention” refers to the combination of various strategies that individuals can choose at different times in their lives to reduce their risks of sexual exposure to the virus.

SUGGESTED GUIDANCE

Guidance Point 1:

Development of Biomedical HIV Prevention Interventions

Given the human, public health, social, and economic severity of the HIV epidemic, countries, development partners, and relevant international organisations should promote the establishment and strengthening of sufficient capacity and incentives to foster the early and ethical development of additional safe and effective biomedical HIV prevention methods, both from the point of view of countries and communities in which biomedical HIV prevention trials take place, and from the point of view of trial sponsors and researchers.

Given the global nature of the epidemic, the devastation being wrought in some countries by it, the fact that biomedical HIV preventive interventions may be the best long term solution by which to control the epidemic, especially in low- and middle-income countries, and the potentially universal benefits of effective biomedical HIV prevention tools, there is an ethical imperative for global support to develop these modalities. This effort requires intense international collaboration and coordination over time among countries with scientific expertise and resources, and countries in which candidate products could be tested but whose infrastructure, resource base, and scientific and ethical capacities may need strengthening. Though potential HIV prevention tools such as microbicides, vaccines, herpes simplex virus-2 (HSV-2) suppression/treatment, female-initiated barrier methods, index partner treatment, antiretroviral drugs for prophylaxis, and biomedical interventions for injecting drug users should benefit all those in need, it is imperative that they benefit the populations at greatest risk of exposure to HIV. Thus, HIV prevention

product development should ensure that products are appropriate for use among such populations, among which it will be necessary to conduct trials; and, when developed, they should be made available and affordable to such populations.

Because HIV prevention product development activities take time, are complex, and require infrastructure, resources, and international collaboration,

- countries who may sponsor trials and countries who may participate in trials should include biomedical HIV prevention product development in their national HIV prevention and control plans.
- countries who may participate in trials should assess how they can and should take part in biomedical HIV prevention product development activities either nationally or on a regional basis, including identifying resources, establishing partnerships, conducting national information and research literacy campaigns, strengthening their scientific and ethical sectors, and including biomedical HIV prevention product research to complement current comprehensive HIV prevention programming.
- development partners, international agencies, and governments should make early and sustained commitments to allocate sufficient funds to make biomedical HIV preventive interventions a reality. This includes funds to strengthen ethical and scientific capacity in countries where multiple trials will have to be conducted, to enhance South–South as well as North–South capacity building and technology transfer, and to purchase and distribute future biomedical HIV prevention tools.
- potential trial sponsors and countries who may participate in trials should establish partnerships with each other, initiate community consultations, support the strengthening of necessary scientific and ethical components, and make plans with all stakeholders for equitable distribution of the benefits of research.

Guidance Point 2:

Community Participation²

To ensure the ethical and scientific quality and outcome of proposed research, its relevance to the affected community, and its acceptance by the affected community, researchers and trial sponsors should consult communities through a transparent and meaningful participatory process which involves them in an early and sustained manner in the design, development, implementation, and distribution of results of biomedical HIV prevention trials.

It is highly important to engage in consultations with communities who will participate in the trial from the beginning of the research concept, in an open, iterative, collaborative process that involves a wide variety of participants and takes place under public scrutiny. Participatory management benefits all parties; helps ensure smooth trial functioning; and builds community capacity to understand and inform the research process, raise concerns, and help find solutions to unexpected issues that may emerge once the trial is underway. Failure to properly and genuinely engage communities early in the stages of research planning may result in an inability to properly conduct and complete important trials. Furthermore, active community participation should strengthen not only local ownership of the research, but also the negotiating power of communities, the research skills of local investigators, and the social leverage that can be useful in areas of the society beyond the research trial site. Communities of people affected by research should conversely play an active, informed role in all aspects of its planning and conduct, as well as the dissemination of results. Achieving meaningful participation requires

² Consider further the UNAIDS/AVAC Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials (2007).

the acknowledgement of structural power imbalances between certain communities and researchers and/or research sponsors, and striving to overcome them. In practical terms, this means putting in place outreach and engagement measures to support participation. Special attention should be paid to the inclusion and empowerment of women for active involvement throughout the research process, as well as to the representation of populations at higher risk of HIV exposure, including adolescents.

The nature of community involvement should be one of continuous mutual education and respect, partnership, and consensus-building regarding all aspects of the testing of potential biomedical HIV prevention products. A continuing forum should be established for communication and problem-solving on all aspects of the HIV prevention product development programme from phase I through phase III and beyond (see **Guidance Point 6**), to the distribution of a safe and effective HIV prevention tool. All participating parties should define the nature of this ongoing relationship. It should include appropriate representation from the community on committees charged with the review, approval, and monitoring of a biomedical HIV prevention trial. As with investigators and sponsors, communities should also assume appropriate responsibility to assure the successful completion of the trial and the product development programme.

Defining the relevant community for consultation and partnership is a complex and evolving process that should be discussed with relevant local authorities. As more groups and people define themselves as part of the interested community, the concept needs to be broadened to civil society so as to include advocates, media, human rights organizations, national institutions and governments, as well as researchers and community representatives from the trial site. Partnership agreements should include a clear delineation of roles for all stakeholders and should specify the responsibilities of sponsors, governments, community, advocacy organizations, and media, as well as researchers and research staff.

Appropriate community representatives should be determined through a process of broad consultation. An agreement should be reached among stakeholders about the definition of a “community” and ways that it can be effectively represented in decision-making early in the design of the study protocol. The process for determining who will be credible and legitimate community representatives should be addressed through a preliminary consultative process between researchers and key members of the community in which the research is proposed to take place. Members of the community who may contribute to development of a safe and effective HIV prevention product include representatives of the research population eligible to serve as research participants, other members of the community who would be among the intended beneficiaries of the developed product, relevant non-government organisations, persons living with HIV, community leaders, public health officials, and those who provide health care and other services to people living with and affected by HIV.

Formal community meetings need to be organised in a way that facilitates the active participation of those most affected by the research being proposed. The principal investigator and site research staff should work with representatives of affected communities to identify needs related to their participation, including logistical requirements such as transportation to the meeting site. Educational materials should be designed in an accessible format, using easy to understand language. Adequate consultation and full participation in the planning process will require more than formal community meetings, as such meetings may alienate some people or be inaccessible to others due to the timing or the format. The principal investigator and site research staff should make efforts to reach out to affected communities, meeting at community centres, workplaces, and other frequented locations. In both formal and informal consultations, the timing and length of the meetings should be convenient for community members, using approaches that facilitate two-way communication with two goals in mind: (1) to identify and

understand community concerns and needs, as well as their knowledge and experience, and (2) to clearly describe the research being proposed, related benefits and risks, and other practical implications.

Participation of the community in the planning and implementation of a biomedical HIV prevention product development strategy can provide at least these favourable consequences:

- information regarding the health beliefs and understanding of the study population
- information regarding the cultural norms and practices of the community
- input into the design of the protocol
- input into the design of an effective recruitment and informed consent process
- insight into the design of risk reduction interventions
- effective methods for disseminating information about the trial and its outcomes
- information to the community-at-large on the proposed research
- trust between the community and researchers
- equity in eligibility criteria for participation
- equity in decisions regarding level of care and treatment and its duration, and
- equity in plans for releasing results and distributing safe and efficacious HIV prevention products.

Researchers may lack the requisite language, communication skills, and experience to respond to community concerns, while communities may be unfamiliar with research concepts, such as “double blind” and “cause and effect”, and may not define HIV prevention research as a priority. This underscores the need for “joint literacy”, whereby researchers and community groups become sufficiently fluent in the requisite concepts and language to work productively together. Research literacy programs that include ethics training for study staff can facilitate and enhance cooperation with civil society groups.

Guidance Point 3:

Capacity Building

Development partners and relevant international organisations should collaborate with and support countries in strategies to enhance capacity so that countries and communities in which trials are being considered can practice meaningful self-determination in decisions about the scientific and ethical conduct of biomedical HIV prevention trials and can function as equal partners with trial sponsors, local and external researchers, and others in a collaborative process.

Countries and communities who choose to participate in biomedical HIV prevention trials have the right, and the responsibility, to make decisions regarding the nature of their participation. Yet disparities in economic wealth, scientific experience, and technical capacity among countries and communities have raised concern about possible exploitation of participant countries and communities. The development and testing of biomedical HIV preventive interventions requires international cooperative research, which should transcend, in an ethical manner, such disparities. Real or perceived disparities should be resolved in a way that ensures equality in decision-making and action. The desired relationship is one of equals, whose common aim is to develop a long-term partnership through South-South as well as North-South collaboration that sustains site research capacity.

Factors that affect perceptions of disparity in power between sponsors and the countries and communities in which research takes place may include, but are not limited to, the following:

- level of the proposed community's economic capacity and social power;
- community/cultural experience with and/or understanding of scientific research and of their responsibilities;

- research staff experience with and/or understanding of the community/culture;
- local political awareness of the importance and process of biomedical HIV prevention trials;
- local infrastructure, personnel, and technical capacity for providing comprehensive HIV health care and treatment options;
- ability of individuals in the community to freely provide informed consent, in light of cultural norms, socio-economic status, gender, and other social factors (see **Guidance Points 16 and 17**);
- level of experience and capacity for conducting ethical and scientific review (see **Guidance Point 4**); and
- local infrastructure, personnel, and laboratory and technical capacity for conducting the proposed research.

Strategies to overcome these disparities and empower communities could involve:

- characterisation of the local epidemic through prevalence/incidence studies and behavioural assessments
- scientific exchange, and knowledge and skills transfer, between sponsors, researchers, communities and their counterparts, and the countries in which the research takes place, including in the field of social science;
- capacity-building programmes in the science and ethics of biomedical HIV prevention research by relevant scientific institutions and local and international organisations;
- support to develop national and local ethical review capacity (see **Guidance Point 4**);
- support to communities from which participants are drawn regarding information, education, and consensus-building in biomedical HIV prevention trials;
- early involvement of communities in the design and implementation of HIV prevention product development plans and protocols (see **Guidance Point 2**); and
- development of laboratory capacity that can support health care provision as well as research.

In the coming years, there will be increasing demands on clinical sites so that national governments, sponsors, and researchers should think

about how to sustain site capacity and retain research staff expertise. Site development may build capacity for a specific trial or enhance the ability of a site to compete more broadly for a range of trials. Given the long time frames of biomedical HIV prevention research, special attention to communication and transparency is needed in order to build and maintain trust with participating communities, and to sustain site capacity even after the end of a trial.

Guidance Point 4:

Scientific and Ethical Review

Researchers and trial sponsors should carry out biomedical HIV prevention trials only in countries and communities that have appropriate capacity to conduct independent and competent scientific and ethical review.

Proposed biomedical HIV prevention trial protocols should be reviewed by scientific and ethical review committees that are located in, and include membership from, the country in which researchers wish to operate. Trials should register with an international trial registry prior to committee review as a condition of approval. Community representatives should also be involved in review of the trial protocol to insure that the research is informed by the concerns and priorities of the community in which the study is to take place. This process ensures that the proposed research is analysed in scientific and ethical terms by individuals who are familiar with the conditions prevailing in the potential research population. Reviewers should not allow research to begin unless the potential benefits of the experimental intervention outweigh the risks to participating individuals and groups. Independent ethical review of research protocols ensures public accountability and also minimizes concerns with regard to researchers' conflicts of interest because of relationships with the sponsors or pressures from those promoting the research. The scientific and ethical review should involve individuals with training in science, statistics, ethics, and law.

Some countries do not currently have the capacity to conduct independent, competent, and meaningful scientific and ethical review. If the country's capacity for scientific and ethical review is judged to be inadequate, the sponsor should be responsible for ensuring that adequate structures for scientific and ethical review prior to the start of the research are developed in the country in which the trial will take place — or the research should not take place. Care should be taken to minimise the potential for conflicts of interest, while providing assistance in capacity-building for scientific and ethical review. Capacity-building in scientific and ethical review may also be developed in collaboration with international agencies, organisations within the host country, and other relevant parties.

Scientific and ethical review prior to approval of a trial protocol should take into consideration these issues:

- ✓ the value and validity of the research protocol
- ✓ community participation and involvement
- ✓ risk-benefit ratio
- ✓ recruitment strategies and methods
- ✓ inclusion and exclusion criteria and screening of participants
- ✓ informed consent procedures and written information sheets
- ✓ provision of support, care, and treatment to participants, and in the community
- ✓ respect for potential recruits and enrolled trial participants and protection of participants' rights
- ✓ confidentiality, privacy, and data protection measures
- ✓ prevention of stigma and discrimination
- ✓ sensitivity to gender
- ✓ procedures for monitoring enrolled participants
- ✓ quality assurance and safety control
- ✓ plans for post-trial distribution and benefit sharing.

*Guidance Point 5:***Clinical Trial Phases**

As phases I, II, and III in the clinical development of a biomedical HIV preventive intervention all have their own particular scientific requirements and specific ethical challenges, researchers and trial sponsors should justify in advance the choice of study populations for each trial phase, in scientific and ethical terms in all cases, regardless of where the study population is found. Generally, early clinical phases of biomedical HIV prevention research should be conducted in communities that are less vulnerable to harm or exploitation, usually within the sponsor country. However, countries may choose, for valid scientific and public health reasons, to conduct any trial phase within their populations, if they are able to ensure sufficient scientific infrastructure and sufficient ethical safeguards.

The initial pre-clinical phase in the development of a biomedical HIV prevention product entails research in laboratories and among animals. The transition to a phase I clinical trial in which testing involves the administration of the product to human subjects to assess safety, and in the case of vaccines to assess immunogenicity, is a time when risks may not yet be well-defined. Hence, specific infrastructures are often required in order to ensure the safety and care of the research participants at these stages. For these reasons, the first administration of a candidate biomedical HIV prevention product in humans should generally be conducted in populations which are not at risk of HIV acquisition, usually in the country of the trial sponsor.

Clinical trial researchers have been designing trials that fall somewhere between phase II (expanded safety and immunogenicity) and phase III (large scale trials to assess efficacy) – called phase IIB trials, or proof of concept trials. Phase IIB trials may provide an indication of

an experimental candidate's efficacy but are less costly in terms of money, time, and number of trial participants. However, such phase IIB trials are not designed to provide enough information for regulatory approval at the end of the trial for an HIV prevention product subject to regulation; instead, these trials test the general concept of the candidate product and efficiently filter out products that lack efficacy. Eventually, a phase III trial would have to be conducted to develop a useable and licensable HIV product.

There may be situations where low- and middle-income countries choose to conduct phases I/II and/or IIB and III among their populations that are relatively vulnerable to risk and exploitation. For instance, this could occur where an experimental HIV vaccine is directed primarily toward a viral strain that does not exist in the trial sponsor's country but does exist in the country in which it is proposed the trial be conducted. Conducting phase I/II trials in the country where the strain exists may be the only way to determine whether safety and immunogenicity are acceptable in that particular population, prior to conducting a phase III trial. Another example might be a country that decides that, due to the high level of HIV risk to its population and the gravity of HIV prevalence in the country, it is willing to test a biomedical HIV prevention product concept that has not or is not being tested in another country. Such a decision may result in obvious benefits to the country in question if an effective product is eventually found. If phase I or phase II trials are conducted in the country intending to participate in an eventual phase III trial, if phases I and II are satisfactory, this may assist in building capacity for phase III trial conduct, including increasing levels of research literacy in the population.

Establishing a biomedical HIV prevention product development programme that entails the conduct of some, most, or all of its clinical trial components in a country or community that is relatively vulnerable to harm or exploitation is ethically justified if:

- the product is a vaccine anticipated to be effective against a strain of HIV that is an important public health problem in the country;
- the country and the community either have, or with assistance can develop or be provided with, adequate scientific and ethical capability and administrative and health infrastructure for the successful conduct of the proposed research;
- community members, policy makers, ethicists, and investigators in the country have determined that their residents will be adequately protected from harm and exploitation, and that the biomedical HIV prevention product development programme is necessary for and responsive to the health needs and priorities in their country; and
- all other conditions for ethical justification as set forth in this document are satisfied.

In cases in which it is decided to carry out phase I or phase II trials first in a country other than the trial sponsor's country, due consideration should be given to conducting them simultaneously in the country of the trial sponsor, where this is practical and ethical. Also, as a general rule, phase I/II trials that have been performed in the country of the trial sponsor should ordinarily be repeated in the community in which the phase III trials are to be conducted, although this may not be needed, particularly in situations in which a product has demonstrated unexpectedly high efficacy.

Guidance Point 6:

Research Protocols and Study Populations

In order to conduct biomedical HIV prevention trials in an ethically acceptable manner, researchers and relevant oversight entities should ensure that the research protocol is scientifically appropriate and that the interventions used in the experimental and control arms are ethically justifiable.

In order to be ethical, clinical trials of novel biomedical HIV prevention tools should be based on scientifically valid research protocols, and the scientific questions posed should be rigorously formulated in a research protocol that is capable of providing reliable responses. Valid scientific questions relevant to biomedical HIV prevention product development are those that seek:

- to gain scientific information on the safety and efficacy (degree of protection) of candidate biomedical HIV prevention products, and, in the case of vaccine candidates, immunogenicity (ability to induce immune responses against HIV);
- to determine correlates or surrogates of safety and protection in order to better characterise and elicit protective mechanisms;
- to compare different candidate products; and
- to test whether biomedical HIV prevention products effective in one population are effective in other populations.

Furthermore, the selection of the research population should be based on the fact that its characteristics are relevant to the scientific issues raised; and the results of the research will potentially benefit the selected population. In this sense, the research protocol should:

- justify the selection and size of the research population from a scientific point of view;

- demonstrate how the candidate biomedical HIV prevention intervention being tested is expected to be beneficial to the population in which testing occurs;
- establish safeguards for the protection of research participants from potential harm arising from the research (see **Guidance Point 11**); and
- be sensitive to issues of privacy and confidentiality in recruitment procedures (see **Guidance Point 17**).

Guidance Point 7:

Recruitment of Participants

In order to conduct biomedical HIV prevention trials in an ethically acceptable manner, participation of individuals should be voluntary and the selection of participating communities and individuals must be fair and justified in terms of the scientific goals of the research.

Selection and recruitment of communities and individuals for participation in a trial must be fair and should create a research climate which shows respect for all persons. This encompasses decisions about who will be included through the formulation of inclusion and exclusion criteria, and through the strategy adopted for recruiting participants. The scientific goals of the study should be the primary basis for determining the individuals who will be recruited and enrolled. Individuals should not be excluded from the opportunity to participate without a good scientific reason or a susceptibility to risk that justifies their exclusion. Social and cultural factors should be considered to determine the vulnerability within the community of individuals who are either included or excluded. In particular, gender-sensitive approaches are key when designing recruitment procedures and special attention needs to be paid to the inclusion or exclusion of pregnant women.

In some situations, voluntariness of participation may be compromised by factors such as social marginalization, political powerlessness, and economic dependence. Voluntariness of participation may also be compromised where there is a cultural tradition of men holding decision making authority in marital relationships, parental control of women, and other forms of social subjugation and coercion (see **Guidance Point 9**). In some communities, it is customary to require the authorization of a third party, such as a community elder or head of a family, in order for investigators to enter the community or to approach individuals. However, the third party only gives permission to invite individuals to participate and such authorisation or influence must not be used as a substitute for individual informed consent. Trials should not be conducted where truly voluntary participation and ongoing free informed consent cannot be obtained. Authorisation by a third party in place of individual informed consent is permissible only in the case of some minors who have not attained the legal age of consent to participate in a trial. In cases where it is proposed that minors will be enrolled as research participants, specific and full justification for their enrolment must be given, and their own assent or consent must be obtained in light of their evolving capacities (see **Guidance Point 10**).

*Guidance Point 8:***Vulnerable Populations**

The research protocol should describe the social contexts of a proposed research population (country or community) that create conditions for possible exploitation or increased vulnerability among potential trial participants, as well as the steps that will be taken to overcome these and protect the rights, the dignity, the safety, and the welfare of the participants.

By definition, HIV prevention research must follow the epidemic. In order to test if a biomedical HIV prevention intervention works, large numbers of individuals at high risk for HIV infection must be recruited for clinical trials. Sites based in communities with mature HIV epidemics have lower incidence rates and may be most appropriate for safety studies. Sites in communities with younger epidemics may be better suited for efficacy trials. However, participating communities and populations, particularly for large-scale efficacy trials, will generally be characterized by multiple vulnerabilities. The same factors that put these individuals at higher risk for exposure to HIV also make them vulnerable to cultural exclusion, social inequality, economic exploitation, and political oppression. Examples of populations that may have an increased vulnerability include women, children and adolescents, men who have sex with men, injecting drug users, sex workers, transgender persons, indigenous populations, the poor, the homeless, and communities from resource-poor settings in high-income and low- and middle-income countries. At the same time, it is precisely these populations who stand to benefit most from the successful development of a new biomedical HIV prevention product or method. For these reasons, it is imperative to ensure protection of the rights of participants in biomedical HIV prevention trials, and respect for their dignity, safety, and welfare.

Decision-making around conducting a biomedical HIV prevention trial needs to consider in what ways the trial might increase or decrease vulnerabilities. On the one hand, a trial might increase a participant's risk of exposure to stigmatisation and discrimination if it highlights a population's increased vulnerability to HIV exposure. On the other hand, a trial might decrease vulnerability, if it empowers the community or provides tangible assistance to participants, for example by improving the accessibility, affordability, and quality of appropriate healthcare services in the community. A social and political analysis should be carried out early on in planning the research process, to assess determinants of vulnerability, such as poverty, gender, age, ethnicity, sexuality, health, employment, education, and legal conditions in potential participating communities. Findings from this analysis should inform the design of research protocols, which should be sensitive to emerging information on incidental risks of social harm throughout the course of a trial. Research protocols might also include ongoing independent monitoring of a trial in relation to its impact on the vulnerabilities of communities participating in the study (see **Guidance Point 17**).

The *particular* aspects of a social context that create conditions for exploitation or increased vulnerability should be described in the research protocol, as should the safeguards and measures that will be taken to prevent and overcome them. In some potential research populations (countries or communities), conditions affecting potential vulnerability or exploitation may be so severe that the risk outweighs the benefit of conducting the study in that population. In such populations, biomedical HIV prevention trials should not be conducted.

Sensitivity to factors of potential vulnerability, including language and cultural barriers, should inform procedures for recruiting and screening potential participants, informed consent processes, and the support, care, and treatment that participants receive in relation to the trial. If a scientifically appropriate population is identified as vulnerable to social harm, specific safeguards should be implemented to protect individual participants, such as ensuring confidentiality, the freedom to decline joining the study and the right to withdraw at any time without penalty.

Guidance Point 9:

Women

Researchers and trial sponsors should include women in clinical trials in order to verify safety and efficacy from their standpoint, including immunogenicity in the case of vaccine trials, since women throughout the life span, including those who are sexually active and may become pregnant, be pregnant or be breastfeeding, should be recipients of future safe and effective biomedical HIV prevention interventions. During such research, women's autonomy should be respected and they should receive adequate information to make informed choices about risks to themselves, as well as to their foetus or breastfed infant, where applicable.

Women throughout the life span, including those who are sexually active and may become pregnant, be pregnant or be breastfeeding, should be recipients of future safe and effective biomedical HIV prevention products and therefore should be eligible for enrolment in biomedical HIV prevention trials, both as a matter of equity and because in many communities throughout the world women, particularly young women, are at higher risk of HIV exposure. Therefore, the efficacy of candidate biomedical HIV prevention products, and their immunogenicity in the case of vaccines, should be established for women. Clinical trials should also be designed with the intent of establishing the safety of candidate biomedical prevention products for the health of the woman and, where applicable, her foetus, breastfed infant and, in the case of vaginal or rectal microbicides, her sexual partners.

If the safety of the biomedical HIV prevention product for a pregnant woman and her foetus has not been established prior to commencement of the trial, women who become pregnant in the course of the trial might be discontinued from using the product, which would

result in loss to follow-up of the participating women. Therefore the question of whether a safety study for pregnant women should be conducted early on in the research, at the stage when a candidate has sufficient promise to advance into a Phase IIB or Phase III efficacy trial in adults or only after the trial product has been shown to be effective should be discussed and resolved on a case-by-case basis early on in the planning of the research design. In any event, researchers should monitor adverse events among pregnant women and women who become pregnant in the course of the trial, notably in the case of a miscarriage, to determine their relatedness to the biomedical HIV preventive intervention.

The most notable data gap in the evaluation of some prevention methods, particularly in phase I and II trials, is adequate evaluation of safety and efficacy among women. Barriers for women participating in trials include contraceptive requirements, issues related to current or future fertility, concerns about safety for the foetus, and fear of being labelled as being at higher risk for HIV exposure. Also, women present issues of particular complexity with regard to recruitment and informed consent. In some cultures, women and girl adolescents may not be able to exercise true autonomy in light of the influence of their parents or sexual partners (see **Guidance Point 7**). In others, young people may be more informed than their parents, and their view and their parents' or partners' views on their participation may differ. Further, the need for HIV testing or pregnancy testing to assess eligibility for inclusion in a trial may raise difficult issues regarding the maintenance of appropriate confidentiality. Researchers and research staff should improve recruitment strategies by anticipating and finding solutions to address and overcome these barriers (see **Guidance Point 7**). Appropriate reproductive and sexual health counselling and ancillary services, including family planning, should be provided to trial participants.

Although the enrolment of pregnant or breastfeeding women complicates the analysis of risks and benefits, because both the woman and the foetus or infant could be benefited or harmed, such women should be viewed as autonomous decision-makers, capable of making an informed choice for themselves and for their foetus or child. In order for pregnant women to be able to make an informed choice for their foetus/breastfed infant, they should be duly informed about any potential for teratogenesis and other known or unknown risks to the foetus and/or the breastfed infant. If there are risks related to breastfeeding, women should be informed of the availability of nutritional substitutes and other supportive services. Researchers should observe and study the positive and adverse effects on the children of these women. They should maintain pregnancy registries to collect data on outcomes of pregnancies that inadvertently occur during the trial, follow-up babies born to women participants, and take due measures for protection of privacy and personal data. In the particular case of trials of prevention of mother-to-child transmission, both women and their infants who became infected should also be assessed for the development of antiretroviral resistance and its potential for effects on subsequent therapeutic options.

*Guidance Point 10:***Children and Adolescents**

Children and adolescents should be included in clinical trials in order to verify safety and efficacy from their standpoint, in addition to immunogenicity in the case of vaccines, since they should be recipients of future biomedical HIV preventive interventions. Researchers, trial sponsors, and countries should make efforts to design and implement biomedical HIV prevention product development programmes that address the particular safety, ethical, and legal considerations relevant for children and adolescents, and safeguard their rights and welfare during participation.

Children³, including infants and adolescents, should be eligible for enrolment in biomedical HIV preventive intervention trials, both as a matter of equity and because in many communities throughout the world children are at a higher risk of HIV exposure. Infants born to HIV-infected mothers are at risk of becoming infected during birth and during the postpartum period through breastfeeding. Many adolescents are also at higher risk of HIV infection due to sexual activity, lack of access to HIV prevention education and means, and through injecting drugs with non-sterile equipment.

Therefore, biomedical HIV prevention product development programmes should consider the needs of children for a safe and effective preventive intervention; should research the legal, ethical, and health considerations relevant to their participation in biomedical trials; and should enrol children in clinical trials designed to establish safety and efficacy for their age groups, including establishing immunogenicity in the case of vaccines, if their health needs and the ethical considerations relevant to their

³ As defined by the Convention on the Rights of the Child, Article 1: "... a child means every human being below the age of eighteen years unless, under the law applicable to the child, majority is attained earlier."

situation can be met. Those designing biomedical HIV prevention product development programmes that might include children should do so in consultation with groups dedicated to the protection and promotion of the rights and welfare of children, both at international and national levels.

It is generally understood that adolescents, prior to initiation of sexual activity and exposure to any risk of HIV infection, will be the primary target for any public health intervention involving a successful biomedical intervention. In the case of HIV vaccine candidates and other products requiring licensure that would have an indication for use in both adolescents and adults, it is imperative that there be no delays in achieving simultaneous licensure/registration for both populations. It is therefore recommended in such cases, that adolescents be included in trials as soon as possible when a candidate has sufficient promise to advance into a Phase IIB or Phase III efficacy trial in adults (see **Guidance Point 5**). The use of bridging studies designed for safety (and, in the case of an HIV vaccine, immunogenicity testing), but not including HIV infection as a primary endpoint could be considered as an alternative for younger adolescents, to be carried out in parallel to Phase III trials in adults.

There may be legal barriers to enrolment of younger adolescents into a clinical trial in which sexual activity is directly linked to achieving primary endpoints. It is imperative that trials are conducted in compliance with the protective laws and regulations applicable at the trial sites, including those related to legal age of consent, the age of majority, the legal age for consensual sex, legal obligations to report abuse or neglect, and other aspects which may have an impact on the conduct of biomedical HIV preventive intervention trials. Thus, undertaking a survey of applicable local laws is an essential requirement to ensure required compliance prior to making plans for such trials in a particular country.

As with all other trials involving children, the permission of a parent or legal guardian is required along with the assent of the child. Unless exceptions are authorised by national legislation, consent to participate in a biomedical HIV preventive intervention trial must be secured from the parent or guardian of a child who is a minor, before the enrolment of the child as a participant in a vaccine trial. The consent of one parent is generally sufficient, unless national law requires the consent of both. Every effort should be made to obtain assent to participate in the trial also from the child according to the evolving capacities of the child, and his or her refusal to participate should be respected.

In some jurisdictions, individuals who are below the age of consent are authorised to receive, with their active consent and without the consent or awareness of their parents or guardians, such medical services as therapeutic abortion, contraception, treatment for illicit drug use or alcohol abuse, and treatment of sexually transmitted infections. In some of these jurisdictions, such minors are also authorised to consent to serve as participants in research in the same categories without the agreement or the awareness of their parents or guardians, provided the research presents no more than “minimal risk”. However, such authorisation does not justify the enrolment of minors as participants in biomedical HIV prevention trials without the consent of their parents or guardians.

In some jurisdictions, some individuals who are below the general age of consent are regarded as “emancipated” or “mature” minors and are authorised to consent without the agreement or even the awareness of their parents or guardians. These may include those who are married, parents, pregnant or living independently. When authorised by national legislation, minors in these categories may consent to participation in biomedical HIV prevention trials without the permission of their parents or guardians.

During the informed consent process, it is recommended that investigators conduct the consent (parent) and assent (adolescent) processes separately. This would ensure confidential counselling for the adolescent and protect the adolescent's privacy (see **Guidance Point 18**). It is also important to inform adolescents of all the elements disclosed to an adult, and to determine that the adolescent understands what s/he is assenting to (see **Guidance Point 16**). The consent process and document should describe clearly what information regarding the adolescent will or will not be disclosed to the parent(s) or legal guardian, as well as what medical or other services will be provided to the adolescent, as needed, without further parental permission.

In some settings, children may have guardians who have not been legally recognized by a court as such. Adolescents who do not have parents or legally recognized guardians should not be automatically excluded from participation in a biomedical HIV preventive intervention trial. Participation could be considered for such adolescents who wish to participate in a trial, as long as a protective ethical oversight mechanism can be established in compliance with the local law. In addition, mechanisms should be established for an independent evaluation of the capacity of such adolescents to give informed consent.

*Guidance Point 11:***Potential Harms**

Research protocols should specify, as fully as reasonably possible, the nature, magnitude, and probability of all potential harms resulting from participation in a biomedical HIV prevention trial, as well as the modalities by which to minimise the harms and mitigate or remedy them.

Participation in biomedical HIV prevention trials may involve physiological, psychological, and social risks. Participation in a complicated, lengthy trial involving intensely intimate matters, repeated HIV testing, and exposure to culturally different scientific and medical concepts may cause anxiety, stress, depression, as well as stress between partners in a relationship. Legal regulations for HIV disclosure may require partner notification when volunteers test-positive or trial participants acquire HIV infection (see **Guidance Point 18**).

Participation, if it becomes publicly known, may also cause stigma and discrimination against the participant if s/he is perceived to be HIV-infected or at higher risk of acquiring HIV infection, particularly for women and adolescents, and already marginalised populations. HIV has been associated with illicit behaviour, including injecting drug use, sex work, and sexual relations between men, as well as with behaviours which may not be condoned such as premarital or extra-marital sexual activity. Discrimination can take the form of accusations or abuse, can affect marriage prospects, and can result in social ostracism, job loss, denial of property or inheritance rights, or the denial of health care. Women may be at heightened risk of domestic violence as a result of trial participation. Trial sponsors, countries, and researchers should ensure that trials take place only in communities where confidentiality can be maintained and where participants will

have access to, and can be referred to, ongoing psycho-social services, including counselling, social support groups, and legal support.

In addition to the risk of negative social impact of participation in HIV-related research, particularly for individuals and communities which are already stigmatised and marginalised, physical injuries may be sustained due to research-related activities, such as blood drawing or other medical interventions. Injections may result in pain, occasional skin reactions, and possibly other biological adverse events, such as fever and malaise.

In trials of microbicides, vaccines, HSV-2 suppression and antiretroviral pre-exposure prophylaxis, there may be unknown risks to a foetus exposed to the product. In trials of prevention of mother-to-child transmission, mothers may develop antiretroviral drug resistance and may transmit resistance virus to their infants; infants may develop resistance during prophylaxis while breastfeeding.

Despite previous safety testing of microbicide products, trial participants and/or sexual partners who are exposed to the product may experience adverse effects, including those which may increase risk of HIV acquisition. In the case of microbicides containing antiretroviral drugs, there may be systemic absorption of active ingredients with possible development of antiretroviral resistance should HIV infection be acquired. In pre-exposure prophylaxis trials, individuals who acquire HIV infection may develop resistance to the antiretroviral drug in the experimental product.

Vaccine trial participants who are exposed to HIV may have a greater risk of developing established infection, or of progressing more rapidly once infected, than if the vaccine had not been administered. If a vaccine candidate elicits a positive HIV antibody test in the absence of HIV infection, i.e. a “false positive” HIV test, negative social consequences similar to those that may exist for those actually HIV-infected may result. Informed consent procedures should

include discussion of the possibility of testing HIV antibody-positive without being HIV-infected. Laboratory techniques that differentiate vaccine-induced antibodies and actual HIV infection should be provided at the clinical site and trial participants should be provided with necessary documentation to demonstrate that their participation in an HIV vaccine trial may be the cause of their HIV-antibody seropositivity. Consideration should be given to appointing an ombudsperson who can intervene on behalf of participants with outside parties, if necessary and requested.

The potential for adverse reactions to a candidate biomedical HIV prevention product, as well as possible injuries related to the conduct of biomedical HIV prevention research, should be described, as far as possible, in the research protocol and fully explained in the informed consent process. Both the protocol and the informed consent process should describe the nature of medical treatment to be provided for injuries, as well as compensation for harm incurred due to research-related activities and the process by which it will be decided whether an injury will be compensated. HIV infection acquired during participation in a biomedical HIV prevention trial should not be considered a compensable injury unless directly attributable to the prevention product being tested itself, or to direct contamination through a research-related activity. In addition to compensation for trial-related biological/medical injuries, appropriate consideration should be given to compensation for social or economic harms.

*Guidance Point 12:***Benefits**

The research protocol should provide an accurate statement of the anticipated benefit of the procedures and interventions required for the scientific conduct of the trial. In addition, the protocol should outline any services, products, and other ancillary interventions provided in the course of the research that are likely to be beneficial to persons participating in the trials.

Clinical research inherently entails uncertainty about the degree of risk and benefits, with earlier phases of research having greater uncertainty. Proceeding to a human trial can be justified only if there is reasonable biological plausibility that a product could be safe and effective, and there is equipoise – meaning that whether a product will actually work is unknown but there is a favourable risk–benefit ratio. Only anticipated benefits of study-related procedures required for the safe and scientific conduct of the trial should be considered in the risk–benefit analysis, that is, only health care benefits derived directly from the study design. Extraneous benefits, such as payment or ancillary services, such as HIV risk-reduction interventions or reproductive health care services, should not be considered in the risk–benefit analysis. Scientific and ethical review committees must be satisfied that the potential risks to individual subjects are minimized, the potential benefits to individual participants are enhanced, and the potential benefits to individual participants and the community are proportionate to or outweigh the risks.

There should be an ongoing iterative consultative process to facilitate local or national decision-making about the appropriate level of support, care, and treatment provided to potential and enrolled participants. Some of the activities related to the conduct of HIV biomedical HIV prevention trials which may benefit those who participate may actually be rights. At a minimum, participants should:

- have regular and supportive contact with health care workers and counsellors throughout the course of the trial;
- receive comprehensive information regarding HIV transmission and how it can be prevented;
- receive access to HIV testing and prevention methods, including male and female condoms, sterile injecting equipment, and sexual and reproductive health care services; and
- have access to a pre-defined care and treatment package for HIV-related illness if they become HIV-infected while enrolled in the trial (see **Guidance Point 14**).

Participants should also receive reimbursement for travel and other expenses related to participation in a biomedical HIV prevention trial. In recognising the time and inconvenience their participation entails, the appropriate form and level of extraneous non-health incentives will depend on the local economic and social context.

Some have contended that to promise antiretroviral treatment to HIV prevention trial participants who become infected would constitute an undue inducement to participate in the trial. That supposition is most unlikely, since biomedical HIV prevention trials enrol healthy people, not individuals who are already sick and need treatment. If anything, the possibility of being protected from acquiring HIV by the preventive method itself could conceivably be considered an undue inducement; however, if that were the case, clinical trials of preventive methods could never be ethically carried out. Concerns that any form of care and treatment promised to participants in research on biomedical HIV preventive interventions could be an undue inducement are unwarranted.

Some may argue that provision of state-of-the-art prevention, care, and treatment services for participants introduces local inequalities and is therefore unjust when non-participants do not receive those services. However, all scale-up programmes involve temporary inequalities in the community until universal access can be attained. Achieving a perfect system of equal justice is a long-term process.

*Guidance Point 13:***Standard of Prevention**

Researchers, research staff, and trial sponsors should ensure, as an integral component of the research protocol, that appropriate counselling and access to all state of the art HIV risk reduction methods are provided to participants throughout the duration of the biomedical HIV prevention trial. New HIV-risk-reduction methods should be added, based on consultation among all research stakeholders including the community, as they are scientifically validated or as they are approved by relevant authorities.

The ethical principle of beneficence obligates researchers and sponsors to maximise benefits and minimise risks to participants in clinical trials. This obligation pertains not only to the preventive method being studied, but also to reducing the risk that any trial participant will acquire HIV infection during a biomedical HIV prevention trial.

Protocols for HIV prevention research obligate researchers to provide the full range of information and services for risk reduction, although they vary in defining the package of services and modes of delivery. If the study aims to test a product by comparing its additive effects to those of routinely practiced prevention, in all cases this prevention standard should be defined in the study protocol as well as in informed consent documents. If researchers are unable to guarantee that this standard is met, it is unethical to conduct the proposed trial.

Risk-reduction packages should include provision for family planning, pregnancy and childbirth services. Women may become pregnant during a trial. Some of these women may wish to carry the babies to term, some might have miscarriages, and some might elect to have therapeutic abortions. Researchers should guarantee that all communities engaged in biomedical HIV prevention trials have state of the art reproductive health care services.

Researchers should engage appropriate stakeholders in tailoring the design, implementation, and oversight of risk-reduction interventions addressing the specific needs and risks of trial participants in a given community. Trial sponsors, researchers, and advocates should continue efforts to resolve ongoing conflicts about legal constraints on public health practice, such as the provision of therapeutic abortion services or the provision of appropriate risk-reduction interventions for trial participants who inject drugs, including sterile injecting equipment and drug substitution treatment.

All trial participants should receive HIV risk-reduction counselling, as well as access and entitlement to proven prevention methods, and to post-exposure prophylaxis in the event of a known likely exposure. Comprehensive counselling should include the basic principles of safer sexual practice and safer injecting practices, as well as education concerning general health and treatment of sexually transmitted infections (STIs), reproductive health (contraception, pregnancy care etc.), and strategies to reduce domestic violence. Investigators should provide trial participants appropriate access to male and female condoms, sterile injecting equipment, medical substitution therapy such as methadone or buprenorphine maintenance, and treatment for other STIs. All trial participants should also be counselled at the beginning of a biomedical HIV prevention trial regarding the potential benefits and risks of post-exposure prophylaxis with antiretroviral medication, and how it can be accessed in the community. Ways should be explored with local authorities to provide trial volunteers and participants with information about HIV prevention and treatment services available in the community. Referral mechanisms should be established and follow-up mechanisms instituted to ensure quality case management services.

The technique, frequency, and message content of counselling sessions should be agreed upon by the community–government–investigator–sponsor partnership, and should be based upon reliable information about the prevailing social and behavioural characteristics of the study population. The provision of HIV risk reduction counselling should be monitored to ensure quality and to minimise the potential conflict of interest between risk-reduction goals and the biomedical prevention trial’s scientific goals. Consideration should be given to providing counselling through an agency or organisation that is independent of the investigators in order to prevent any real or perceived conflict of interest. If such an arrangement is put in place the researchers and community must ensure that the services are of a high enough standard to meet the trial’s ethical obligations. Local capacity may need to be developed to provide such services in a culturally suitable and sustainable fashion, guided by the best scientific data. National and international research oversight groups should evaluate the pros and cons of independent organizations implementing risk-reduction interventions in biomedical HIV prevention trials; where such efforts are warranted and feasible, they should be undertaken and rigorously evaluated.

Mechanisms for negotiation among all research stakeholders, including the community, about the standards for enhancement of the risk-reduction package during the trial as new biomedical HIV prevention modalities are scientifically validated or are approved by national authorities need to be set in the study protocol. Negotiations should take into consideration feasibility, expected impact, and the ability to isolate the efficacy of the biomedical HIV modality being tested, as other prevention activities improve.

Guidance Point 14:

Care and Treatment

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. 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.

The obligation on the part of sponsors and investigators to ensure access to HIV care and treatment, including antiretroviral treatment, for participants who become infected derives from some or all of three ethical principles. The principle of *beneficence* requires that the welfare of participants be actively promoted. The principle of *justice as reciprocity* calls for providing something in return to participants who have volunteered their time, been inconvenienced or experienced discomfort by enrolling in the trial. The principle of *justice*, meaning *treating like cases alike*, requires that trial participants in high-income and low- and middle-income countries be treated equally regarding access to treatment and care.

A consensus on the level of care and treatment that should be provided to trial participants has emerged in recent years with increasing accessibility of antiretroviral treatment in low- and middle-income countries, based on strong commitments from countries, development partners and multilateral organizations; dramatic decreases in drug prices; and evidence that treatment programmes in resource-poor settings are feasible and sustainable. There is consensus that sponsors need to ensure access to internationally recognised optimal care and treatment regimens, including antiretroviral therapy, for participants who become HIV infected during the course of the trial. There is also agreement that prevention trials ought to contribute constructively to the development of HIV service provision in countries participating

in biomedical HIV prevention research, for the sustainable provision of care and treatment after the completion of a trial.

The provision of antiretroviral treatment to trial participants who acquire HIV infection during the trial requires planning for logistics and implementation. Most such participants will not need antiretroviral treatment until years after sero-conversion. However they may benefit from a comprehensive care and prevention package including cotrimoxazole prophylaxis, isoniazid, nutritional advice, and positive prevention counselling. Biomedical HIV prevention trials should undertake to support such therapy until individuals become eligible for the national program of care and treatment in their country. Countries should include participants in biomedical HIV prevention trials in their priority list for access to antiretroviral treatment under the “Towards Universal Access” programme.

Trial sponsors and researchers should collaborate with governments in low- and middle-income countries to explore, develop, and strengthen national and local capacity to deliver the highest possible level of HIV prevention, care, and treatment services through strategic investment and development of trial-related resources. In most situations, no one stakeholder should bear the entire burden of providing resources for such services and the central responsibility for delivery should lie with local health systems.

Decisions on how these obligations are to be met are best made for each specific trial through a transparent and participatory process that should involve all research stakeholders before a trial starts to recruit participants (see **Guidance Point 2**). This process should explore options and determine the core obligations applicable to the given situation, in terms of the level, scope, and duration of the care and treatment package, equity in eligibility to access services, and responsibility for provision and delivery. Agreements on who will finance, deliver, and monitor care and treatment should be documented. All stakeholders should recognize that this is a critically important and highly uncertain

area that requires all partners to commit themselves to experimentation and the careful documentation of approaches, successes, and failures.

Clinical trials should be integrated into national prevention, treatment, and care plans so that services provided through clinical trials or arrangements brokered for trial participants serve to improve the health conditions of both the trial participants and the community from which they are drawn, and support and to strengthen a country's comprehensive response to the epidemic. Strengthening mechanisms to provide care, treatment, and support for people who acquire HIV infection during the course of a trial will assist in ensuring referral and care provision for people who are deemed ineligible at recruitment to a biomedical HIV prevention trial because they already have HIV infection.

A care and treatment package should include, but not be limited to, some or all of the following items, depending on the type of research, the setting, and the consensus reached by all interested parties before the trial begins:

- counselling
- preventive methods and means
- treatment for other sexually transmitted infections
- prevention of mother to child transmission
- prevention/treatment of tuberculosis
- prevention/treatment of opportunistic infections
- nutrition
- palliative care, including pain control and spiritual care
- referral to social and community support
- family planning
- reproductive health care for pregnancy and childbirth
- home-based care
- antiretroviral therapy

*Guidance Point 15:***Control Groups**

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 scientifically validated in comparable populations or approved by relevant authorities.

Aside from male circumcision, a biomedical HIV prevention intervention with proven efficacy in preventing HIV acquisition or HIV-related disease does not currently exist. Therefore, until an efficacious intervention is developed, the use of a placebo control arm could be ethically acceptable in appropriately designed protocols, such as three-arm trials. For example, there may be compelling scientific reasons which justify the use of a placebo rather than a known effective biomedical HIV intervention in the following instances:

- An effective HIV vaccine exists but it is not known to be effective against the virus that is prevalent in the research population.
- The biological conditions that prevailed during the initial trial demonstrating efficacy of a biomedical HIV prevention product are so different from the conditions in the proposed research population that the results of the initial trial are not generalizable and cannot be directly applied to the research population under consideration.
- A microbicide shown to be effective for vaginal intercourse may not be effective for rectal intercourse.
- Effectiveness of an intervention in one population may not be reproduced in the context of another population if the success of the intervention is strongly related to behaviour or behavioural modification and conditions of product utilisation. For example, a partially effective, coitally dependent microbicide evaluated among women in stable partnerships may not be generalizable to women with multiple casual partners.

Guidance Point 16:
Informed Consent

Each volunteer being screened for eligibility for participation in a biomedical HIV prevention trial should provide voluntary informed consent based on complete, accurate, and appropriately conveyed and understood information before s/he is actually enrolled in the trial. 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. Informed consent, with pre- and post-test counselling, should also be obtained for any testing for HIV status conducted before, during, and after the trial.

Biomedical HIV prevention trials require informed consent for all components of participation at a number of stages. The first stage consists of screening candidates for eligibility for participation in the trial. The screening process involves interviews on personal matters, such as sexual behaviour and drug use, which are protected by a right to privacy. To guarantee this right, secrecy and confidentiality must be strictly observed and appropriate measures of personal data protection should be set in place (see **Guidance Point 18**). The screening process also involves medical tests (such as blood draws, pregnancy and HIV tests, vaginal examinations, and a general physical examination), the results of which are also private and should be kept in confidence. Informed consent should be obtained to undergo this screening process, based on a full divulgence of all material information regarding the screening procedures, as well as an outline of the biomedical HIV prevention trial in which they will be invited to enrol, if found eligible. Fully informed consent should also be given for the test for HIV status, which should be accompanied by pre- and post-test counselling and, if the result is HIV positive, referral to clinical and social support services.

The second stage at which informed consent is required occurs once a person is judged eligible for enrolment. That individual should then be given full information concerning the nature and length of participation in the trial, including the risks and benefits posed by participation, so that s/he is able to give informed consent to participate. Time should be allowed to consider participation, discuss with others such as partners, and ask questions. Candidates should also be informed of their rights as participants, including the right to confidentiality (see **Guidance Point 18**) and the right to refuse to participate or to withdraw at any time from the study without penalty.

Once enrolled, efforts should then be made throughout the trial to obtain assurance that the participation continues to be on the basis of free consent and understanding of what is happening. Informed consent, with pre- and post-test counselling, should also be given for any repeated tests for HIV status. Throughout all stages of the trial and consent process, there should be assurance by the investigator that the information is understood by the participant before consent is given. Informed consent is a process, not just a piece of paper to be read and signed. The information should be presented in appropriate forms and languages, including written information sheets. In addition, there should be oral communication of information, especially for participants who may be illiterate, and standardized tests for assessment of comprehension, where necessary.

In addition to the standard content of informed consent prior to participation in a biomedical HIV preventive intervention trial, each prospective participant must be informed, using appropriate language and technique, of the following specific details:

- the reasons they have been chosen as prospective participants, including whether they are at higher risk of HIV exposure;
- that the biomedical HIV prevention product is experimental and it is not known that it will prevent HIV infection or disease, and

further, when such is the case, that some of the participants will receive a placebo instead of the candidate HIV prevention product through random assignment;

- that they will receive counselling concerning how to reduce their risk of HIV exposure and access to risk-reduction means (in particular, male and female condoms, clean injecting equipment, and where relevant, male circumcision); and that, in spite of these risk-reduction efforts, some of the participants may become infected, particularly in the case of phase III trials where large numbers of participants at higher risk of HIV exposure are participating;
- the specific risks for physical harm, as well as for psychological and social harm (see **Guidance Point 11**), the types of treatment and compensation that are available for harm, and the services to which they may be referred should harm occur;
- the nature and duration of care and treatment that is available, and how it can be accessed, if they become infected with HIV during the course of the trial (see **Guidance Point 14**);
- the collection, use, and period of storage of biological samples and specimens provided by participants, and the options for their disposal at the conclusion of the trial, including the option to refuse to allow use of such samples or specimens beyond the scope of the specific trial in which they have participated.
- the use, confidentiality, period of storage, and disposal of personal data including genetic information, including the option to refuse to allow use of such data beyond the scope of the specific trial in which they participated (see **Guidance Point 18**).

Special Measures

Researchers and research staff should take special measures to protect persons who are, or may be, limited in their ability to participate voluntarily in a biomedical HIV prevention trial due to their social or legal status. The presumption is that all adults are legally competent to give informed consent to participate in a biomedical HIV prevention trial. However, there are several categories of

persons who are legally competent and who have sufficient cognitive capacity to consent, but who may have limitations in their freedom to make independent choices (see **Guidance Point 8**).

The following are individuals or groups who should be given extra consideration with regard to their ability to voluntarily participate in biomedical HIV prevention trials:

- persons who are junior or subordinate members of hierarchical structures, who may be vulnerable to undue influence or coercion and may fear retaliation if they refuse cooperation with authorities, including members of the armed forces, students, government employees, prisoners, and refugees;
- persons who engage in illegal or socially stigmatised activities, who are vulnerable to undue influence and threats presented by possible breaches of confidentiality and action by law enforcement authorities, including sex workers, injecting drug users, and men who have sex with men;
- persons who are impoverished or dependent on welfare programmes, who are vulnerable to being unduly influenced by offers of what others may consider modest material or health inducements.

Those who plan, review, and conduct biomedical HIV prevention trials should be alert to the problems presented by the involvement of such persons, and take appropriate steps to ensure meaningful and independent ongoing informed consent, and to respect their rights, foster their well being, and protect them from harm. Such steps would include community involvement in the design of recruitment and informed consent processes, along with the sensitization and training of research staff and counsellors on these issues.

*Guidance Point 17:***Monitoring Informed Consent and Interventions**

Before a trial commences, researchers, trial sponsors, countries, and communities should agree on a plan for monitoring the initial and continuing adequacy of the informed consent process and risk-reduction interventions, including counselling and access to proven HIV risk-reduction methods.

Methods for monitoring the adequacy of recruitment and informed consent processes, including evaluation of participants' comprehension of information, should be designed and agreed upon by the community-government-investigator-sponsor partnership. The value of informed consent depends primarily on the ongoing quality of the process by which it is conducted and not solely on the structure and content of the informed consent document. The informed consent process should be designed and monitored to empower participants to allow them to make appropriate decisions about continuing or withdrawing from the study. Special attention should be given to ensure that individuals are aware of their right to withdraw from a trial without any penalty, and that they are actually free to do so. Similarly, there are many ways in which risk-reduction interventions (counselling and access to means of HIV prevention) can be conducted, with some methods being more effective than others in conveying the relevant information and in reducing risk of HIV exposure for different individuals and study populations.

Monitoring should include quality assurance of gender- and culture-sensitive counselling services, appropriate procedures for adolescents, and evaluation of the impact of the trial on the vulnerabilities of the communities involved in the study. It should also cover the welfare of participants throughout the trial, including when discontinuing participation in case of adverse reactions, untoward events or changes in clinical status.

Consideration should be given to expansion of the responsibilities of the clinical trial monitor to include adherence to the recruitment and informed consent processes and to counselling standards. Consideration could also be given to the appointment of an independent ombudsperson who would handle any complaints from participants related to the conduct of the trial and suggest appropriate responses.

The appropriateness of such plans should be determined by the scientific and ethical review committees that are responsible for providing prior and continuing review of the trial. This recommendation supplements the usual guidelines for the monitoring of biomedical HIV prevention trials for safety and compliance with scientific and ethical standards and regulatory requirements.

Guidance Point 18:

Confidentiality

Researchers and research staff must ensure full respect for the entitlement of potential and enrolled participants to confidentiality of information disclosed or discovered in the recruitment and informed consent processes, and during conduct of the trial. Researchers have an ongoing obligation to participants to develop and implement procedures to maintain the confidentiality and security of information collected.

A lot of information about a volunteer or a study participant is collected as part of participation in HIV vaccine and prevention research. Very personal information, like sexual behaviour, drug use, HIV status, medical conditions or even association with the trial could be highly stigmatizing and might be socially harmful if other people wrongly discover it. It is therefore of particular importance in biomedical HIV prevention trials that researchers and research staff commit to keeping confidential all personal information of all

potential and enrolled participants so as to minimise the likelihood of such harm, and that they explain to volunteers and participants what measures they will be taking to protect privacy and personal information, and what limitations may exist on their ability to do so.

All participants are entitled to confidentiality of information disclosed or discovered in the recruitment and informed consent processes, and during conduct of the trial. Community involvement should not compromise the confidentiality of study participants. This is of particular importance with respect to participants from vulnerable populations, women and adolescents, who may be socially susceptible to stigma and discrimination (see **Guidance Points 8, 9, 10**). There may be specific exceptions to the duty of confidentiality for legal or ethical reasons, but those exceptions should be prospectively identified and disclosed to the participant during the informed consent process.

Legal exceptions to the duty to maintain confidentiality might exist, for example, where disclosure is mandated by a court order or where there is a duty to report to public health authorities. In the case of children and adolescents, reporting of abuse and neglect might be required under child protection laws. Similarly, the reporting of domestic violence might be a legal duty. Trial staff should be trained to identify instances where there is such a mandatory reporting duty.

Breach of confidentiality might also be warranted on ethical grounds, so as to notify sexual partners. For example, where women participate in microbicide trials, there may be unknown risks of harm to male partners. The sponsor and researcher should have a mechanism for them to come forward to report possible negative consequences and make sure that they are notified of such, preferably by the female participants. Likewise, when participants become HIV positive, sexual partners at ongoing risk should be notified for referral to testing programmes and treatment facilities. However, researchers and research staff should be sensitive to the possibility of domestic violence as a result of partner notification.

Researchers have an ongoing obligation to participants and the host community to develop and implement procedures to protect

the privacy of participants and to maintain the confidentiality of information collected. Such procedures might include interviewing participants outside, where they cannot be overheard, or permitting participants to not receive HIV test results. Both health care workers and research staff may need explicit training on how to maintain confidentiality. To protect confidentiality, workers in the clinic or programme setting where recruitment is taking place should first ask potential volunteers whether they would be willing to speak to a researcher who will provide information about trial participation. In the case of adolescents being recruited for endpoint efficacy trials, researchers should inquire whether their parents are aware of their sexual behaviour and explain that parental permission will be required for enrolment. In the case of media interest in the trial, research staff members should also advise participants of possible negative impact that may result from public exposure. Community advisory boards may need training to enable members to interview about the trial in ways that do not compromise the duty of confidentiality owed to individual participants or jeopardise their right to privacy.

Research may involve collecting and storing private and sensitive data relating to individuals and communities including data derived from biological samples (see **Guidance Point 16**). Measures of data protection are of major importance in large-scale studies such as HIV prevention trials which establish large databases to integrate clinical data and monitor public health effect. Decisions regarding which personal data are to be collected and stored must be based on the requirements of the trial design and the medical needs of participants. Personal identifiable data should be collected only by people who have signed a confidentiality agreement. The collection of personal identifiable data should be kept at a minimum and such data should not be stored longer than necessary. Procedures should be in place to monitor the use of the system where the data are stored in order to detect potential or actual security threats. Systematic guidance on security of data can be found in the UNAIDS *Interim Guidelines on Protecting the Confidentiality and Security of HIV Information* (2007).

*Guidance Point 19:***Availability of Outcomes**

Researchers should inform trial participants and their communities of the trial results. During the initial stages of development of a biomedical HIV prevention trial, trial sponsors and countries should agree on responsibilities and plans to make available as soon as possible any biomedical HIV preventive intervention demonstrated to be safe and effective, along with other knowledge and benefits helping to strengthen HIV prevention, to all participants in the trials in which it was tested, as well as to other populations at higher risk of HIV exposure in the country.

To respect and recognize the contribution of trial participants and their communities to clinical research, researchers should inform them of the trial results, whether the biomedical intervention does or does not demonstrate efficacy, or the trial is stopped prematurely. 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.

Given the severity of the HIV epidemic, it is imperative that sufficient incentives exist, both through financial rewards in the marketplace and through public subsidies, to foster development of safe and effective biomedical HIV prevention products and ensure that they are produced and made readily and affordably available to the communities and countries where a product is tested, as well as to populations at higher risk of HIV exposure in other countries.

Some argue that fair benefits to the population where clinical trials are conducted need not include making successful products of the

research available to that population. Critics contend that it is paternalistic to specify the benefits, and that the country may identify other benefits that have a higher priority. However, given the severity of the epidemic (see **Guidance Point 1**) making a successful HIV biomedical HIV prevention product or intervention reasonably available to the population where it was tested can be sustained as a basic ethical requirement.

Health and research communities building biomedical HIV prevention product development programmes should initiate before trials commence, and carry on through the course of the research, a process of discussion and negotiation about how products will be made available, along with other benefits resulting from the research, if the HIV preventive intervention is effective. This discussion should include representatives from relevant country stakeholders, such as representatives from the executive branch, health ministry, local health authorities, and relevant scientific and ethical groups, as well as from community advisory mechanisms and other key stakeholders. It should address issues such as payments, royalties, subsidies, technology and intellectual property, as well as distribution costs, channels and modalities, including delivery strategies, target populations, demand estimates, and supply chain requirements.

The discussion concerning availability and distribution of an effective biomedical HIV prevention product should further engage the national government, international organisations, development partners, representatives from wider affected communities, local authorities, international and regional non-governmental organizations, and the private sector. In addition to considering financial assistance to make biomedical HIV prevention products available, these partners should respect and help build governments and community capacity to negotiate for and implement distribution plans. Among the issues to be addressed well in advance to ensure that novel effective HIV prevention products have the greatest impact are:

- ongoing communication with regulatory agencies to ensure timely licensing of proven safe and efficacious methods which require regulatory approval;
- planning for capacity building, including transfer of technology, to mass produce an effective biomedical HIV prevention product well in advance of product licensing, so as to minimize manufacturing delays;
- preparing in advance the infrastructures needed for delivery of new products through existing distribution systems for other currently available HIV prevention products, such as male and female condoms or prophylaxis for mother-to-child transmission;
- instituting advance purchase commitments or other supply side planning to deliver product for those people and populations which it has been agreed should enjoy first the benefit of a new proven HIV prevention intervention.

Guidance Point 20:
People Who Inject Drugs⁶

Researchers and sponsors should include people who inject drugs in biomedical HIV prevention trials in order to verify safety, efficacy, and effectiveness from their standpoint, including immunogenicity in the case of vaccines.⁷ As with other key populations at higher risk of HIV exposure, providing people who inject drugs with access to proven, effective HIV preventive interventions is a public health imperative. Researchers and trial sponsors should engage meaningfully with people who inject drugs and with other stakeholders to overcome the complex legal, ethical, and regulatory challenges to the participation in biomedical HIV prevention trials of people who inject drugs. Trial conduct that is ethical is informed by the latest scientific evidence on proven HIV prevention strategies and ensures that participants' human rights, safety, and welfare are protected.

People who inject drugs are at higher risk of acquiring blood-borne HIV infection, primarily because legal and logistical barriers impede safer use and access to sterile injecting equipment, such as needles, syringes, and cookers. They are also at increased risk of acquiring and transmitting HIV through unsafe sexual practices. Women who inject drugs or who have a partner who injects drugs are at higher risk of HIV acquisition and of subsequent mother-to-child transmission during pregnancy, labour and delivery, and breastfeeding.

As with other key populations at higher risk of HIV acquisition, people who inject drugs should be included and meaningfully engaged (see **Guidance Point 2**) in biomedical HIV prevention trials

⁶ A broader term that may apply is 'people who use drugs' when such use places individuals at higher risk of HIV exposure through non-injecting modes of transmission.

⁷ As for all the guidance points in this document, this guidance point is relevant to trials of various behavioural HIV prevention methods and structural interventions.

in order to ensure that novel prevention methods are proven to be safe, efficacious, and accessible for them, both as a matter of equity and as an expression of their right to health. However, prevention trials involving people who inject drugs pose complex challenges that may increase risks to trial participants. Researchers and sponsors should take necessary steps to safeguard participants' human rights, safety, and welfare.

The ethical principles of beneficence and non-maleficence obligate researchers and sponsors to maximize benefits and minimize risks to participants in HIV clinical trials. This is done in part by providing appropriate counselling and facilitating access to proven state-of-the-art risk reduction methods (see **Guidance Point 13**). However, legal barriers, punitive law enforcement practices, logistical challenges, and discrimination often prevent people who inject drugs from accessing proven risk reduction methods, including those comprising the comprehensive package of core interventions for people who inject drugs developed by WHO, UNODC, and UNAIDS.⁸ In addition to provision of condoms, counselling, and access to educational information on safe-injecting practices, a key risk reduction method for people who inject drugs is the use of sterile injecting equipment. Where there are insurmountable barriers to ensuring access to sterile needles and syringes for all trial participants, HIV prevention trials among people who inject drugs should not proceed.

Any enhancements to the standard of prevention package as the scientific evidence base evolves should be discussed by all trial stake-

⁸ WHO, UNODC and UNAIDS. Technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users. Geneva, 2009. The comprehensive package comprises the following nine interventions: needle syringe programmes; drug dependence treatment (opioid substitution treatment and other); HIV testing and counselling; antiretroviral therapy; prevention and treatment of sexually transmitted infections; programmes with condom for people who inject drugs and their sexual partners; targeted information, education, and communication for people who inject drugs and their sexual partners; diagnosis and treatment of or vaccination for viral hepatitis; prevention, diagnosis, and treatment of tuberculosis.

holders, taking into consideration feasibility, expected impact, and the ability to isolate the efficacy of the biomedical HIV modality being tested (see **Guidance Point 13**).

In settings where possession of injecting equipment is illegal, researchers and sponsors should negotiate agreements with relevant authorities so that risk reduction tools provided through the trial as standard of prevention do not increase the risk that trial participants will be subject to punitive legal or extra-legal enforcement measures. Some potential risk reduction interventions, for example opioid substitution treatment, may carry additional risks for trial participants, such as breaches of privacy and confidentiality resulting from mandatory registration. Further, painful opioid withdrawal may result if medication-assisted substitution programmes are not properly resourced and sustained. Trial sponsors, researchers, and advocates should continue efforts to determine whether and how risks associated with components of the risk reduction package could be mitigated in both the short- and long-term.

Researchers and sponsors have an obligation to ensure access to HIV care and treatment, including antiretroviral therapy, for participants who acquire HIV infection during a trial (see **Guidance Point 14**). In addition, they should negotiate with national and local governments appropriate referral mechanisms to ensure access to care and treatment for those people who volunteer to participate in a trial but who are screened out as ineligible when they are found to be HIV-positive. In some settings, people who inject drugs may not be seen as priority recipients for limited HIV care and treatment resources. The ethical principle of justice requires *both* that researchers and sponsors work to ensure that access to care and treatment is available to people who inject drugs as equitably as it is to others in the community and that the standard of care and treatment is equivalent across high-, low- and middle-income countries (See **Guidance Point 14**). Care for trial participants may also involve the treatment of co-morbidities, ready

access to overdose management, and provision of a safe place of respite where participants may be provided with food or other amenities. A transparent and inclusive process to determine logistics and to assign responsibilities for providing this care package should take place in advance of trial commencement.

People who inject drugs suffer several layers of vulnerability (see **Guidance Point 8**). Criminalization of their drug use renders them vulnerable to punitive, often harsh, law enforcement practices including incarceration. They may experience additional vulnerability because of generalized stigma and discrimination, including from some health care professionals and policy-makers; personal mental health issues, preceding or resulting from their drug use; poverty; racism, if they are members of certain racially-defined groups; and marginalization. Gender adds an additional layer of vulnerability for people who inject drugs who are women, men who have sex with men, or people who are transgender or intersex. They may experience increased vulnerability to unprotected sex and unsafe injections, exploitation, discrimination, lack of sensitivity to their specific needs, and under-resourcing of services to meet their needs.

Prior to commencing a trial, researchers and sponsors should conduct formative research to gain understanding of particular contextual challenges and vulnerabilities that people who inject drugs face and to begin building trust with people who inject drugs and their networks. The research protocol should describe the vulnerabilities identified, as well as steps that have been or will be taken to create a safe enabling environment for trial participants. HIV prevention trials should not be conducted where there are insurmountable barriers to ensure safety, protection, and confidentiality of trial participants (see **Guidance Point 18**). For this reason, and because adherence to the principle of autonomy cannot be guaranteed, HIV prevention trials should not be conducted in compulsory drug detention centres.

In many settings around the world, the consequences of being identified as a person who injects drugs are extremely serious. Precautions should be taken to ensure that recruitment and retention are voluntary, and that people's right to confidentiality and privacy is not breached (see **Guidance Point 18**). Recruitment within voluntary drug treatment centres, especially by service providers upon whom people who inject drugs are dependent for on-going care, may pose special problems regarding voluntariness of trial participation. Generally, potential trial participants should not be recruited by their service providers. Where respondent-driven recruitment and other snowball-type recruitment techniques are used, confidentiality should be emphasized to recruiters. Research teams should be trained to identify when a potential participant is unable to make a voluntary, informed decision about trial participation. Being under the influence may alone not be sufficient reason to assume lack of capacity to decide. Participants should be clearly informed of any limits to confidentiality to which researchers are bound by regulation.

It is not uncommon for people who inject drugs to be incarcerated because of their drug use or for peripheral reasons such as sex work, theft, and vagrancy. Researchers should anticipate that some trial participants could be incarcerated during the course of the trial and should develop an incarceration protocol describing the conditions to be followed to ensure that on-going ethical trial participation is preserved. This should include an option and procedures for voluntary withdrawal of the participant from the trial. The protocol should address confidentiality and voluntariness, access to risk reduction measures while incarcerated, access to a physician, and post-release planning including for consent to re-join the trial. In particular, mechanisms should be put in place to ensure that there is no interruption of antiretroviral therapy or opioid substitution treatment. All relevant stakeholders, including prison authorities, should agree to these provisions in advance of a trial.

In choosing the form of reimbursement for travel and other expenses related to trial participation (see **Guidance Point 12**), researchers should take into consideration participants' preferences and local conditions in order to reach an agreement upon the form and amount of reimbursement. Based on the principle of non-maleficence and concern for undue inducement, caution should be applied when using cash compensations in all clinical trials⁹. Assuming that participants who inject drugs should be provided only with vouchers or in-kind compensation, rather than cash reimbursement equivalent to that provided in trials involving other populations, is discriminatory.

When the biomedical HIV prevention product or intervention tested in a trial is proven to be safe and efficacious, provision should be made to offer it to all trial participants, and to the communities from which they are drawn, following trial completion, regulatory approval, and licencing (see **Guidance Point 19**).

⁹ Council for International Organisations of Medical Sciences (CIOMS) 2002. Ethical Guidelines for Biomedical Research Involving Human Subjects. Guideline 7.

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The Joint United Nations Programme on HIV/AIDS (UNAIDS) brings together ten UN agencies in a common effort to fight the epidemic: the Office of the United Nations High Commissioner for Refugees (UNHCR), the United Nations Children's Fund (UNICEF), the World Food Programme (WFP), the United Nations Development Programme (UNDP), the United Nations Population Fund (UNFPA), the United Nations Office on Drugs and Crime (UNODC), the International Labour Organization (ILO), the United Nations Educational, Scientific and Cultural Organization (UNESCO), the World Health Organization (WHO), and the World Bank.

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