HIV Prevention Trials Network

Ethics Guidance for Research

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List of HPTN Ethics Guidance Points

Guidance point 1. Ensuring high-quality scientific and ethical research

HPTN is committed to developing and maintaining procedures designed to ensure high-quality scientific research and the incorporation of ethical considerations throughout the various stages of HPTN research.

Guidance point 2: Setting research objectives and priorities

Research questions pursued by HPTN should respond to a public health priority in places where the research is being conducted.

Guidance point 3: Engaging communities

In order to ensure that HPTN research is appropriate as well as scientifically and ethically sound, relevant communities will be engaged in a meaningful process that will help guide the research from protocol development to dissemination of results.

Guidance point 4: Building local capacity and partnerships

The conduct of HPTN research should be accompanied, to the greatest extent reasonably possible, with the development of local capacity, such as transferring skills and knowledge and contributing to material infrastructure. Capacity-building efforts should be conducted in close collaboration with local partners.

Guidance point 5: Ethical issues in study design

HPTN investigators will design HIV-prevention research capable of answering important research questions or producing valuable information while minimizing risks and maximizing benefits to study participants and their communities.

Guidance point 6: Consent, assent, permission and re-consent

Each HPTN site involved in a research project will develop, document and implement meaningful informed consent and assent processes. These processes should include assessments of the decision-making capacity of potential participants to give consent, comprehension of relevant information, and re-consent of participants when appropriate.

Guidance point 7: Addressing vulnerabilities

HPTN investigators should be aware of the social, cultural and other factors that may place research participants at heightened risk, and develop procedures and safeguards that appropriately monitor, assess and respond to these factors within the context of research.

Guidance point 8: Ethical review of research

HPTN research protocols will be reviewed by independent ethics review boards in the host country. HPTN should encourage capacity-building of host country ethics review where appropriate.

Guidance point 9: Standard of prevention

In partnership with key stakeholders, HPTN should establish a package of effective, comprehensive and locally sustainable prevention services to be offered to participants in each HPTN study.

Guidance point 10: Standards of care and treatment

In designing the care and treatment package to be provided to study participants, HPTN will meet and strive to exceed local standards of medical services, while taking into account the implications of those standards for research participants, and the potential impact that research-associated care may have on local communities.

Guidance point 11: Independent data safety and monitoring

Particularly in late-stage clinical trials, HPTN should ensure that an independent data monitoring committee is in place in order to help ensure study validity and safety, and assess whether it would be in the interest of study participants to modify or terminate a study. Reliable mechanisms should be established to communicate the results of this independent review to key stakeholders.

Guidance point 12: Disseminating research results

HPTN will plan for the timely communication and dissemination of HIV prevention research results to participants, local communities and other audiences in a manner that promotes comprehension and trust.

Guidance point 13: Sustaining capacity-building and infrastructure into the future

HPTN will work to increase the likelihood that the investments made in capacity-building and infrastructure will continue to provide benefits and opportunities for local communities after the research is over.

Guidance point 14: Continuing care for research participants

HPTN research projects will seek to ensure continuity of care after the termination of research, where appropriate, for participants who have received (and continue to need) medical care and treatment during their involvement in HPTN research.

Guidance point 15: Provision of successful research interventions

HPTN research seeking to establish the efficacy of an intervention must have a preliminary plan regarding the provision of successful interventions to research participants and communities.

Introduction

More than 25 years into the human immunodeficiency virus (HIV) epidemic, more than two million new infections continue to occur each year, and the global burden of disease and death due to HIV is increasing at staggering rate. Morbidity and mortality rates in resource constrained settings have increased despite increasing access to antiretroviral treatment in many parts of the world. From a scientific and public health perspective, research on preventing HIV acquisition and transmission should focus predominately on communities and groups with high HIV incidence. But while HIV prevention research is crucially important for vulnerable populations at heightened risk for HIV, the design and conduct of such research raises considerable ethical challenges, particularly in social contexts marked by poverty, weak health care infrastructures, inequality, discrimination and stigma.

The HIV Prevention Trials Network (HPTN) has the mission of conducting HIV prevention research at the highest scientific and ethical standards. This guidance document aims to facilitate HPTN's mission by raising awareness of the associated ethical considerations, engaging network members at all levels in discussion about those considerations, and facilitating the integration of ethical considerations into the design and implementation of HPTN research. In short, this document has an ethical rather than regulatory purpose. While HPTN research is subject in some settings to procedural review by official bodies such as drug regulatory agencies or government ministries, those processes are to be distinguished from ethics review as understood in this document, i.e. an evaluation of research protocols according to fundamental ethical principles.

This ethics guidance document is organized sequentially according to the different stages of HIV prevention research, from pre-research preparations, to implementation of research protocols, to activities after data collection is completed. Each research stage has

its own set of ethical considerations. This document identifies the primary stakeholder(s) responsible for implementing each of the ethical guidance points described.

Context

In 2003, the HPTN Ethics Working Group produced the *HPTN Ethics Guidance for Research*. A number of developments over the last five years have prompted this revision of the HPTN ethics guidance document.

- *Scientific findings.* Interventions in promising vaccine, sexually transmitted infection (STI) reduction, microbicide and diaphragm trials have had mixed results, but have been disappointing with respect to HIV incidence (van de Wijgert et. al. 2007; Padian et. al. 2007)

- *Challenges in community engagement*. Pre-exposure prophylaxis (PREP) trials in Cambodia and Cameroon were halted after complaints from community groups, accusations from activist organizations and unfavorable media attention (Singh and Mills 2005; Lange 2005)

- *Success of male circumcision trials*. Studies conducted in Uganda, Kenya and South Africa indicated a 60% reduction in relative risk of HIV transmission from women to circumcised men, arguably the most important finding in HIV prevention research since the development of effective drugs to prevent mother-to-child transmission of HIV (Auvert et al. 2005; Gray et. al. 2007; Bailey et. al. 2007)

- *Increased availability of antiretroviral (ART) treatment*. Global initiatives such as the President's Emergency Program for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Malaria and Tuberculosis have sharply increased access to antiretroviral treatment in many parts of the world (Institute of Medicine 2007).

- *Increased attention in the professional literature to ethical issues relevant to HIV prevention research*, including:

    - Ethical obligations towards seroconverters in HIV prevention studies (Weijer and LeBlanc 2006; Macklin 2008)
    - Ethical conduct of HIV prevention research among vulnerable groups, especially adolescents and (pregnant) women (Singh et. al. 2006)
    - Ethical obligations towards non-research participants affected by research activities (Resnik and Sharp 2006; Moodley 2008).

- Concern about responsiveness of research to local needs, against the background of the '90/10 gap' (London and Kimmelman 2008; Shapiro and Benatar 2005).
- Ethical issues at a public health or population level (Wikler and Brock 2007)
- Responsibilities regarding the provision of ancillary care to research participants (Richardson and Belsky 2004; Richardson 2007)
- New approaches to informed consent, including developing, monitoring and evaluating consent processes (Corneli et. al. 2006)

- *Publication of new or revised ethics and regulatory guidance documents relevant to HIV prevention research*, including:

  - Global Campaign for Microbicides (2005) Rethinking the Ethical Roadmap for Clinical Testing of Microbicides
  - UNAIDS (2007) Ethical Considerations in Biomedical HIV Prevention Trials
  - UNAIDS (2007) Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials
  - World Medical Association (2008) Declaration of Helsinki
  - Institute of Medicine (2008) Methodological Challenges in HIV Prevention trials
  - The Common Rule, 45 CFR 46 (revised in 2005)

These developments have been accompanied by empirical activity within the HPTN including:

- Partnering for care and ancillary care obligations (MacQueen et al 2008; MacQueen and May 2008)
- Biological specimens (MacQueen and Alleman 2008)
- Standards of care (MacQueen, Namey et al 2007, MacQueen, Johnson et al 2007)
- Perceptions of ethical challenges within the HPTN (Borasky et al 2009)
- The informed consent process (Woodsong et al, 2006; Sugarman, Corneli et al 2009)

Goals and audience

The central goals of the HPTN ethics guidance document are:

- **To describe traditional and emergent ethical challenges arising in the conduct of HIV prevention research**
- **To act as a useful, practical guide for addressing ethical challenges in all HPTN research, including behavioral studies and non-clinical, community-based trials**
- **To describe reasonable expectations and ethical responsibilities of stakeholders involved in HPTN research**
- **To facilitate incorporation of ethics guidance points into the design, implementation and dissemination of HPTN research**
- **To contribute to local ethics capacity-building at HPTN sites and to a culture of ethics within the HPTN**
- **To be sensitive to the social, cultural, legal and political context where HPTN research takes place**
- **To address gaps, limitations and inconsistencies in existing ethics guidance relevant to HIV prevention research**

Ethical decision-making in research requires a deliberative process. No guidance document, including this one, can eliminate the necessity of identifying relevant issues

and then engaging in a process of description, analysis, and balancing of the ethical tensions inherent to them. Therefore this guidance aims to help ensure that in keeping with its scientific agenda, HPTN ethical decision-making is of the highest quality, despite prevailing uncertainties and the pressure to generate short-term responses to complex, long-term problems.

The HPTN ethics guidance document has a number of intended audiences:

The primary audience is the HPTN, including the Executive Committee, HPTN working groups and protocol teams. The guidance is designed to facilitate their discussions and decision-making in the establishment of research objectives, the selection and development of protocols, and the preparation and implementation of research. For new research protocols, investigators and protocol teams should address the issues raised by the guidance points, and the HPTN review procedures should determine that each point has been adequately addressed. Research protocols currently under development and awaiting approval for implementation should incorporate the actions outlined in the guidance. For research already approved, the protocol team should review the guidance and determine whether there are any discrepancies between the recommended actions and how the research was designed and is being implemented. Where discrepancies exist, the protocol team should develop a plan to systematically address them. If any discrepancies are irresolvable, the efforts made to resolve them should be carefully documented along with justifications for the course of action taken on the issue. The resulting documentation should be reported to the HPTN Scientific Review Committee (SRC) and Prevention Management Group (PMG) and placed in the protocol files at the Coordinating and Operations Center (CORE) and on site.

Collaborating institutions/organizations, community members and community representatives constitute another audience as does the wider group of stakeholders involved in or affected by HPTN research activities, which can include government representatives and agencies, pharmaceutical companies and other industry sponsors,

non-governmental organizations, HIV/AIDS activist groups, trial sponsors, and ethical and scientific review committees. This guidance communicates to these groups that the HPTN intends to conduct ethical research and exactly how the HPTN intends to integrate the ethical considerations into its research design and practice.

In addition to reaching the audiences so connected to HPTN activities, it is hoped that the ethics guidance will be valued as an important contribution to discussions surrounding the ethical aspects of HIV prevention research, and will be useful for other groups and agencies conducting similar research.

Not all points stated in the guidance are of equal strength or significance. There are important differences between points that express ethical obligations and ethical aspirations. If a course of action is described as an ethical obligation (expressed in terms such as 'should', 'must' or 'will'), then normally the action should be done, and while exceptions to that course of action are permissible, these exceptions require a strong ethical justification. For example, gaining informed consent is an ethical obligation, but there may be cases in which consent can be justifiably waived (see Guidance Point 6). In contrast, a course of action expressed in terms of an ethical aspiration (expressed in terms such as 'making good faith efforts') implies that following the course of action is admirable or commendable -- a matter of pursuing important ethical ideals – but is not required. In general terms, the HPTN encourages network members and stakeholders to fulfill their ethical obligations and to pursue ethical aspirations to the greatest extent possible.

The HPTN ethics guidance document seeks to distinguish itself from other existing guidance in three ways. First, it is an expression of ethical ideals the HPTN identifies with and has chosen to pursue, as well as a description how HPTN intends to incorporate ethics into its research activities. It caters to a specific primary audience. Second, unlike some existing guidance, the HPTN guidance is grounded in pragmatism which recognizes both that HIV prevention research must be conducted according to the highest ethical standards and that lofty ethical aspirations will not have a meaningful social impact if

they cannot be applied in the actual research setting that inevitably occurs in the context of political, social, economic, cultural and regulatory constraints and challenges. Third, the guidance aims to be applicable by distinguishing different stages of research and different strengths of ethical requirement, and by identifying those within the HPTN primarily responsible and accountable for fulfilling each guidance point.

Fundamental ethical principles in research

The HPTN is committed to scientifically sound biomedical and behavioral research having the general aim of reducing the incidence of HIV infection. Given the massive suffering caused by the HIV/AIDS epidemic worldwide, this general aim is itself ethically valuable. However, not all approaches are appropriate to achieve this aim, and therefore its pursuit must be tempered by other important ethical considerations. More specifically, the design and implementation of HPTN prevention research should be grounded in the following fundamental ethical principles:

Respect for persons

This value encompasses respect for both the autonomy and dignity of research participants. Respect for autonomy means not only respecting the decisions participants make in the context of research, but helping to empower their decision-making. Respect for dignity means providing research participants with protection from undue risks of harm, stigma, discrimination, and invasion of privacy and bodily integrity.

Researchers must give serious consideration to the cultural values of the community in which research takes place, and to protect it from potential harm where possible. This is sometimes referred to as respect for communities. Research takes place within communities whose ways of life, beliefs, institutions and customs are typically deep-rooted, valued and meaningful to its members. Besides showing respect, community engagement in research development and implementation can enhance the scientific and ethical quality of research studies. Obtaining prior ‘community assent’ for research activities may be regarded as an appropriate expression of respect for community in some

circumstances. However, in particular cases, respect for communities may be justifiably limited by, for example, human rights considerations in communities strongly marked by gender inequalities or discrimination against certain groups.

Beneficence

There is a fundamental obligation that research is designed in such a way as to minimize potential risks of harm to participants and to provide substantive benefits where possible. The risks should be understood broadly to include potential physical, psychological, legal, social and economic risks for both individuals and communities. Research designs must anticipate and incorporate risks and benefits on the basis of the best available scientific knowledge and community consultation.

Social justice

The concept of social justice has many meanings. For the purposes of this document, the term expresses the ethical concerns related to treating people equally, avoiding exploitation, and trying to reduce health disparities. There are vast inequalities in health, income, and power between and within countries worldwide, and HPTN conducts HIV prevention research in many resource-poor settings. In such settings, researchers are challenged to improve health without taking unfair advantage of, or increasing, existing social inequalities. To the extent that it is reasonably possible, researchers and other stakeholders should seek to reduce social inequalities in the domains of health and health care by (for example) building local health-related capacity and infrastructure.

Section I: Ethical issues before research begins

1. Ensuring high-quality scientific and ethical research

HPTN is committed to developing and maintaining procedures designed to ensure high-quality scientific research and the incorporation of ethical considerations throughout the various stages of HPTN research.

Status: Ethical obligation

Responsible and accountable: Network leadership/executive committee

Scientifically sound research

The HPTN Executive Committee, Protocol Teams, the Scientific Review Committee (SRC), and the DAIDS Prevention Science Research Committee (PSRC) have primary responsibility to ensure the scientific soundness of HPTN research through its oversight mechanisms. The established review process is designed to ensure that HPTN research meets the highest scientific standards. In addition, HPTN investigators should conduct formative research if necessary during the site preparation and protocol development phase to help validate measures and data collection strategies or to make study procedures context-specific.

Ethically sound research

Ethically sound design and implementation of research requires thoughtful interpretation of relevant ethical principles in the context of local realities. For most HPTN research, this also requires the careful balancing of disparate local realities at multiple research sites. Ethical review at key points in the research design and implementation process should help to ensure that ethical considerations are addressed in tandem with scientific considerations. The HPTN has instituted the following steps to ensure that ethical considerations are addressed, recognizing that this research will also undergo regulatory review by DAIDS as well as the local IRBs or ERCs established under U.S. and collaborating country regulations:

- *Research Concepts*. Each new concept proposal submitted to the EC for review will include a brief statement indicating ethical considerations associated with the proposed research. The Executive Committee concept review process includes simultaneous review by the EWG chair or the chair's designee. Investigators are encouraged but not required to consult with the EWG in the earliest stages of development of a concept proposal to ensure that ethical challenges are recognized and addressed.
- *Protocol Development*: HPTN researchers are ethically obligated to involve host-country stakeholders, including local researchers, community advisory boards or other community representatives, as early as possible in the protocol development process to ensure responsiveness of proposed research to local health priorities and community values (see Guidance Points 2 and 3). Once a protocol is approved for development, an ethics representative to the protocol team may be appointed by the EWG chair to reduce the likelihood that research timelines will be delayed due to a failure to address the ethical challenges early in the process. The ethics representative must have an appropriate level of expertise in ethics as it relates to the science of the proposed research. This person need not be a member of the EWG. However, s/he should maintain close ties with the EWG and consult with the EWG chair or other members at key points in the protocol development process.
- *Protocol Review*: As part of the SRC protocol review process, an ethics reviewer (and alternate) will be designated by the EWG chair and the HPTN PI. As with the scientific and statistical reviews, the ethics review of new protocols occurs simultaneously with and as an integrated part of the SRC protocol review process, with the SRC chair having responsibility for coordination. To avoid potential biases or conflicts of interest, persons who have served as consultants to or members of the protocol team will not be eligible to serve as ethics reviewers for that protocol. The SRC ethics reviewers will have appropriate expertise in the ethics of HIV prevention research.

- *Protocol Implementation*. HPTN Study-Specific Procedures (SSP) Manuals will address standard ethics domains such as informed consent procedures as well as any special ethical concerns identified during protocol development and approval. Study assessment activities conducted by CORE staff will include attention to ethical concerns identified during protocol development. CORE staff will consult with the EWG to develop checklists to facilitate documentation of ethics-related activities, such as the evaluation of participants' understanding during consent processes. Assessment of ethics-related activities will complement monitoring for compliance with regulatory requirements for human subjects protections performed by DAIDS approved monitors.

2. Setting research objectives and priorities

Guidance point 2: Research questions pursued by HPTN should respond to a public health priority in places where the research is being conducted.

Status: Ethical obligation

Responsible and accountable: Sponsor, executive committee and protocol teams

Most health research, even when it is conducted in developing countries, focuses on diseases and conditions primarily affecting the world's more affluent societies. However, health research that fails to respond to a local health priority, and is hence unlikely to produce any significant benefit to local communities, can be exploitative. HPTN focuses its efforts on research questions that are local health priorities, but which also have potential global relevance for the struggle against HIV/AIDS.

While HIV prevention is a global health priority, not every type of HIV prevention research is a local health priority, even in countries of high HIV incidence. Host-country stakeholders such as representatives of the Ministry of Health, local public health officials, community advisory boards, and non-governmental organizations providing significant health care or services in the local community should be involved early in

protocol development to ensure research relevance. Verification of the extent to which a particular HIV prevention research activity or study responds to a local health priority should be sought from (for example) surveillance data, results of prior public health and behavioral research and government reports.

The underlying ethical concern is that without strong relevance to local needs and strong community engagement and partnership, research objectives may be disconnected from local health priorities, such that the information and/or intervention produced by the research may not significantly benefit the health of the community where the research was performed. If an intervention clearly would not be appropriate or feasible for adoption (should it be proven safe and effective) in the community participating in the trial, or if the information could not be usefully integrated in local health systems, the trial may be unethical and if so it should not be conducted.

3. Engaging communities

Guidance point 3: In order to ensure that HPTN research is appropriate as well as scientifically and ethically sound, relevant communities will be engaged in a meaningful process that will help guide the research from protocol development to dissemination of results.

Status: Ethical obligation

Responsibility and accountable: site Principal Investigators, Community Working Group, HPTN core, network leadership, protocol team

Failure to properly engage and listen to communities early in protocol development and throughout the research process may not only demonstrate disrespect for communities, but may also result in the inability to conduct and complete important HIV prevention research. The HPTN is responsible for outlining steps to develop, maintain, support, and encourage meaningful participation of community representatives in all phases of the

research process. This includes plans for community education, training, recruitment, and participation in network governance and scientific committees. Productive and appropriate research requires 'joint literacy' on the part of both researchers and community groups. Community members may be unfamiliar with some scientific concepts, while researchers may lack the language skills, cultural background and experience to identify and appreciate possible community concerns about proposed research. In order to enhance 'joint literacy', it is strongly recommended that leadership within each research study be appropriately diverse, particularly when a study targets specific social, ethnic or racial groups (e.g. black men who have sex with men).

For the purposes of HPTN research, a community is the group of people who will participate in, are likely to be affected by or have an influence on the conduct of the research. The community may include:

- Parents, children, spouses and siblings, sexual partners, and other significant relations of research participants;
- Local research colleagues who will be partners in the study;
- The group from which research participants will come (e.g. women at risk for HIV who use services in a prenatal clinic, injection drug users in a certain location, or a geographic community);
- The broader geographic community in which the research will be conducted;
- Influential or key individuals from this community (e.g. traditional or governmental leaders, professionals or volunteers who work with HIV prevention or research programs where the research will be conducted, and members of the health care and medical community).

The HPTN should begin community engagement efforts as early as possible in the research development process, including the formulation of research questions if feasible. The HPTN Community Working Group has primary oversight of the process of community engagement, preparedness and consultation. A community advisory

mechanism has been established at each HPTN site, with the most common approach being the creation and maintenance of a Community Advisory Board (CAB). The advisory structure at each site may vary based on local needs. HPTN CABs provide advice on scientific and ethical issues regarding study design, recruitment and the protection of study participants. It may also be appropriate to seek input from agencies and organizations other than the CAB. For example, during proposal development it may be appropriate to meet with a wide range of opinion leaders and stakeholders who potentially stand to benefit from the research to ensure generalizability and utility of the results regionally, nationally, and internationally. When the boundaries of 'community' are widened in this way, the HPTN should develop a clear delineation of the roles and responsibilities of the stakeholders who have been drawn into the process.

Community representatives are important intermediaries between researchers and communities. Community representatives should be credible and legitimate, and selected after consultation and screening with key community members. Appropriate community representatives will vary from site to site, but may include representatives of relevant non-governmental organizations, persons living with HIV, community leaders (such as teachers or religious leaders), health care professionals and persons in the community likely to benefit in the future from the tested intervention.

Dealing with community rumor

In HPTN 039, researchers wanted to extend the shelf life of the antiretroviral study drug for one year. Stability testing was conducted on the drug in order to establish its standard of quality. The government authorities, having considered the results of the stability testing, approved new labeling of the drugs. However, researchers ran into a problem when considering precisely how to label them. Normally, when the shelf life of a drug is extended, a new label is placed on the medication showing both the old and new expiry dates. But since there were already false rumors in Zambia claiming that the government was distributing expired antiretroviral drugs in order to harm the population, this seemed like a bad idea. The community advisory board of HPTN 039 came up with the solution of putting a new label with the new expiry date over the old one, in order not to generate fear and suspicion.

Community representatives and CAB members are responsible for conveying community concerns, beliefs, and norms to site staff, and to serve as a conduit of information between the site and potential research communities. In their capacity as community representatives, they are to put community goals before personal goals, strive to ensure that all significant perspectives are raised (including views of community members or groups that may differ from their own) and help mediate potential disputes among community groups. CAB members are expected to attend local CAB meetings, provide feedback on issues under discussion, voice concerns from communities and research study participants, and disseminate research study information to the local community. They assist in the development and implementation of community education activities, advise the HPTN protocol team in the development of informed consent and research study related documents, and in the development and implementation of recruitment and retention strategies. They also have a responsibility to be in contact with community representatives from other HPTN sites involved in a particular trial, the Principal Investigator, as well as to actively participate in HPTN Community Working Group (CWG), Regional Community Working Group (RWG) and protocol-specific community conference calls.

The Principal Investigator at each site is responsible for sustaining the relationships with community members. The HPTN will support involvement and participation of community members as an integral part of the site operation plan. Each study site will designate a paid staff person to serve as the CAB liaison. Site Community Education staff will facilitate the development of a written plan to actively engage community participation. Site staff and principal investigators are responsible for providing information about concepts, protocols and research in ways that are accessible and appropriate for community representatives. The extent of community engagement may vary depending on the type, stage and length of the proposed research, i.e. less extensive community engagement may be justified for small studies of short duration and minimal risk. In all HPTN studies, it is the responsibility of the PI and site research teams to

ensure that the recommendations of the CAB are not merely gathered, but taken seriously.

4. Building local capacity and partnerships

Guidance Point 4: The conduct of HPTN research should be accompanied, to the greatest extent reasonably possible, with the development of local capacity, such as transferring skills and knowledge and contributing to material infrastructure. Capacity-building efforts should be conducted in close collaboration with local partners.

Status: Aspiration

Responsible and accountable: Sponsors, executive committee, protocol team, principal investigators

Having a locally relevant research objective is only one aspect of research being 'responsive to local needs.' For research to be more broadly responsive, it should ideally be part of a larger program to expand the capacity of health-related social structures in the host community in order to meet its most urgent health needs (London and Kimmelman 2008). When the conduct of HPTN research requires substantial investment in developing clinical and/or laboratory capacity, it is desirable for such services to be available to non-research staff and patients at a locally affordable cost. Ideally, the infrastructure should be developed in ways that make it likely that they can be transferred to local providers who have obtained the appropriate training to use it. HPTN may actively seek support for such transfers through partnerships with developmental aid sponsors and/or local government agencies. Examples of capacity that could be transferred for local use include lab equipment and training of technicians for CD4 and viral load testing for host country ART program use and expanded lab support for STI syndrome management (e.g. syphilis serology, vaginal microscopy, gonorrhea culture). Other possible ways of pursuing the ethical aspiration to build local capacity include scientific exchange and skills transfer in research methods, efforts to raise the quality and

efficiency of health care delivery, and support to strengthen capacity in national and local research ethics review.

Transparent and inclusive negotiations among researchers, community representatives, sponsors and other stakeholders should help to address the ethical aspiration considered by this guidance point. These negotiations should start in the initial planning stages of research. Negotiations should result in the development of reasonable expectations based upon an assessment of local needs while acknowledging the missions of funding agencies. Creative approaches to (and alternative sources of support for) capacity-building efforts should be actively developed.

The aspiration to contribute to local capacity-building is based on the principles of respect for persons and social justice. There are often significant disparities in economic wealth, scientific expertise and technical skills between stakeholders involved in HIV prevention research. Given that the desired relationship between researchers, local investigators and communities is one of collaboration among equals, local capacity-building aims to empower countries and communities to function as equal partners in decision-making processes surrounding HIV prevention trials.

5. Ethical issues in study design

Guidance point 5: HPTN investigators will design HIV-prevention research capable of answering important research questions or producing valuable information while minimizing risks and maximizing benefits to study participants and their communities.

Status: Ethical obligation
Responsible and accountable: Investigators, protocol team

Design questions that are of particular relevance to ethical issues include, but are not limited to those described here: 1) control and comparison groups; 2) selecting study

populations; 3) early phase research; 4) second generation trials; and 5) innovative designs.

Control and comparison groups

The use of control or comparison groups in the design of HIV prevention research is generally scientifically valuable but -- particularly in regard to placebo control groups -- may be ethically controversial. In particular trials, there may be compelling scientific reasons and ethical justifications to include a control and/or comparison arms. For research trials, HPTN requires the selection of control or comparison arms that reflect accepted practices in HIV prevention while concurrently permitting the generation of scientifically valid results and useful data. A prescriptive approach to designing control or comparison arms within HPTN is not feasible due to the complexity of the issue. However, following international norms on clinical equipoise, interventions tested in HIV prevention studies should generally be compared against known effective interventions, and any exceptions to this rule require stringent scientific and ethical justification.

With respect to control arms, proposed research designs must include consideration of the following questions:

- Are there other known effective interventions that could be feasibly implemented to achieve the same goal? Will the experimental intervention be evaluated relative to those interventions?
- Does the trial design preclude or limit the use of any known effective interventions that are or could be made readily available to research participants in the proposed research sites?
- Does the trial design assume that any known effective interventions will not be available at the proposed research sites?
- If other known effective interventions exist, is there evidence to suggest that the experimental intervention will be more efficacious, cost effective, or socially appropriate to implement in the research communities should the research show

the intervention to be meaningfully effective?

- Should the trial have blinded control groups to reduce potential bias or should it include unblinded arms to test effectiveness of the intervention in more real world circumstances?

For trials using control arms, the protocol team should address each of these questions and document the conclusions reached. For research in the developmental phase, this information should be presented as part of the review process and filed with review materials.

Study design, equipoise and evolving knowledge of HIV treatment

In HPTN 052, HIV serodiscordant couples were randomly assigned into two groups: one in which the (HIV positive) index case begins antiretroviral therapy (ART) immediately, and the other in which the index case begins ART only when his or her CD4 count drops below a certain threshold. In order to ethically randomize these couples to these arms, and maintain the equipose of the study, the CD4 range in the inclusion criteria had to be carefully selected. Medical opinion has long been divided on this issue. In the late 1990's, the approach was to start ART even when the patient had a high CD4 count. In the early 2000's, a delayed approach was taken, on account of concerns about drug-related toxicity and drug resistance due to poor adherence. Even today, there is no consensus regarding the optimal CD4 cell count level at which to initiate ART with regard to optimizing disease outcome and survival.

When the 052 protocol was first written in 2002, the CD4 range required for eligibility was 300-500 cells/mm3. This range excluded individuals with high CD4 cell counts (>500), as it was thought that the risk of exposure to drug toxicity was not outweighed by the benefits of ART. The lower limit of the range was chosen so that it was ethical for those randomized to the delayed arm of the study to wait until their CD4 cell count fell to 200 cells/mm3 before initiating ART. In the mid-2000s, data from large cohort studies began to suggest that ART should be initiated in the 250-350 cell/mm3 range, and the World Health Organization revised its guidelines such that ART initiation should be considered in this range. In response to this change, the CD4 inclusion criterion of the protocol was revised to a range of 350-550 cells/mm3; and in the delay arm, ART was initiated when the subject had a confirmed CD4 cell count below 250 cells/mm3.

The point of the research is to compare two groups, one on ART and one not (yet) on ART. However, the researchers did not want anyone to initiate ART at a time when the

risks of the drugs outweighed the benefits, nor did they want to deny ART to anyone who medically requires it. In trying to satisfy both research design and ethical requirements, researchers in HPTN 052 have had to make adjustments to the eligibility criteria of the study in the context of ever-changing knowledge regarding the optimal use of ART in treating HIV.

Selection of study population

Adolescents

Approximately one quarter of new HIV infections occur among young people 15 to 24 years of age, more than half of all new infections are to people younger than 25 years, and young women are affected disproportionately (UNAIDS 2004). A wide range of effective prevention options needs to be developed for this population, and while there are important public health reasons to enroll adolescents in HIV prevention research, their inclusion raises a number of important ethical, social and legal challenges (MacQueen and Karim 2007). Adolescents may be subject to multiple forms of vulnerability due to their immaturity and diminished autonomy, which are often reflected in local laws aiming to safeguard adolescents, including those related to the legal age of consent, consensual sex, and majority as well as legal obligations to report abuse or neglect. Legal restrictions may exclude the possibility of enrolling some at-risk populations, such as adolescents without parents or legal guardians; and legal obligations (e.g. such as the requirement of parental or guardian permission) may limit the inclusion of some important groups such as adolescent girls. In order to reduce risks to (and increase informed participation of) adolescents in HIV prevention research, it is advisable to include adolescents in community advisory boards, involve adolescents (including young men having sex with men) and parents/caregivers as advisors on recruitment and consent processes, and engage with local youth organizations during the protocol development stage.

Pregnant women

Many late-stage biomedical HIV prevention trials are conducted among sexually active women of reproductive age. Despite intensive counseling on family planning, and provision of (or access to) contraceptives, many women participating these trials become pregnant. Regulatory agencies and sponsors generally require that women who become pregnant during trials of new products whose safety and efficacy have not yet been established discontinue the study product.

However, stopping the use of a study product by women who become pregnant has many drawbacks, including negative impacts on statistical power, potential bias of study findings, and loss of important safety and efficacy data on HIV prevention interventions for pregnant women and their fetuses. In areas of high fertility and significant HIV incidence, pregnant women will be exposed to HIV infection. In the future, if an HIV prevention product is tested and approved, pregnant women are likely to use it, even if it has not been proven safe for them or the fetus through clinical trials. Safe inclusion of pregnant women in HIV prevention research should therefore be a scientific and ethical priority.

There are a number of ethical and regulatory issues researchers need to consider when thinking of continuing the use of a study product among women who have become pregnant during an HIV-prevention trial. The study product must have been proven safe in preclinical trials with non-human animals and non-pregnant women, and the risk to the fetus should be minimal unless the research holds out the prospect of a direct benefit to the women or the fetus and the research question could not be answered by any other means (cf. 45 CFR 46.206). Investigators, sponsors, and ethics committees should evaluate the strength of current evidence on the beneficial and harmful effects to both pregnant women and fetuses on a product-by-product basis. They should assess whether there are circumstances in which women who become pregnant can continue to receive the study product, consistent with US Federal regulations and based on the best

obtainable knowledge of the benefits and risks. This sensitive issue clearly requires extensive community engagement. The risks and benefits of continued study participation must be clearly conveyed to pregnant women during the consent and/or re-consent process, and the possible involvement of male partners must be carefully weighed.

Early phase research

Early phase trials often are unlikely to provide any direct benefits to participants and in some cases may expose them to significant risks. Economically disadvantaged participants may join such trials to access ancillary health benefits otherwise unavailable to them. While protection of vulnerable populations is an important consideration, conducting safety trials in resource-poor settings may be ethically justified. For example, the intervention being tested may be directed towards a strain of HIV that is only prevalent in resource-poor countries. Communities with high HIV incidence and prevalence may also want phase I/II trials to take place among its population, as a means of responding to a public health crisis and/or as a way of building infrastructure for a phase III trial and eventual access to a successful trial product. However, the claim that a community wants to conduct phase I/II trials among its vulnerable members should be scrutinized carefully and substantiated with evidence. Researchers must avoid conveying the impression that access to trial products constitutes a benefit of the research, when the effectiveness of the product under study is not yet known.

Second-generation HIV prevention studies

When interventions in first-generation HIV prevention trials suggest some degree of efficacy, this raises significant study design and ethical issues for subsequent second-generation HIV prevention research. For example:

- If a previous study indicates that an intervention may have some efficacy, when is it justified to conduct a similarly designed study of the intervention in another population?

- How many studies demonstrating efficacy of a certain intervention or approach are sufficient to indicate that no further research is scientifically or ethically justified?
- At what point should an intervention be considered sufficiently protective against HIV infection to be included as part of the 'standard of prevention', and as part of the prevention package given to all participants in future HIV prevention trials?

Justification for repeating a trial of an already tested intervention depends upon a number of factors, namely:

1. Strength of evidence from previous trial(s)
2. Population similarity or difference from previous trial(s)
3. Methods used in previous trial(s)

Only if there are significant residual doubts and uncertainties in regard to evidence, population or methodology would it be ethically justified to conduct a new study with the same intervention.

Innovative study designs

HPTN researchers should explore innovative study designs aimed at producing valuable data about HIV prevention interventions with fewer resources and reduced risks to study participants. For example, HIV prevention trials now typically use HIV infection as a clinical endpoint, since there are no reliable markers available to serve as surrogate endpoint. This has practical and ethical implications. Since infection is a relatively rare event in some settings, prevention studies with HIV infection as a clinical endpoint must enroll a very large number of subjects for a considerable time. Testing the efficacy of the intervention depends on some participants becoming HIV infected during the period they are involved in the research. Identification of better assays for early HIV infection could potentially increase the pace and reduce the costs of HIV prevention research, while avoiding the ethical issues raised by use of HIV infection as endpoint. In general , it is ethically desirable for HPTN to develop research designs that are scientifically rigorous, cost-effective and protective of research participants.

6. Consent, assent, permission and re-consent

Guidance point 6: Each HPTN site involved in a research project will develop, document and implement meaningful informed consent and assent processes. These processes should include assessments of the decision-making capacity of potential participants to give consent, comprehension of relevant information, and re-consent of participants when appropriate.

Status: Ethical obligation

Responsible and accountable: Principal investigator

Consent

HPTN is committed to developing and continuously enhancing the quality of its informed consent processes. Informed consent has a number of distinguishable requirements. The prospective participant

- must be competent to engage in decision-making about research participation or, when appropriate, a proxy-decision maker must be sought
- must be provided with sufficient and understandable information about the proposed research, alternatives to participation and the opportunity to raise questions and;
- must express agreement explicitly in some way, by signing or making a personal mark on a form, or by (sometimes witnessed) oral consent

From an ethical perspective, informed consent is only obtained if each of the substantive requirements are met. Since there may be challenges in meeting these requirements in some settings, it is important to design communication methods that are effective and culturally appropriate in content, format and delivery. Where appropriate and feasible, formative research should be used in the pre-enrollment stage to develop a customized

consent process (possibly using alternative media such as pictures, flip charts or video) for a specific study.

The protocol team should also develop mechanisms to evaluate study participants' comprehension of the study. A variety of strategies may be suitable for this purpose, including discussion during the informed consent process, use of informed consent comprehension checklists or quizzes, or interviews with a sub-sample of participants.

In addition, investigators should consider collecting information on participant, staff, and community-wide perceptions of the informed consent process. This information could be collected during site visits providing technical assistance and/or quality assurance tasks, along with review of relevant documents created throughout the course of research implementation. Such activities could complement and draw upon existing monitoring and evaluation efforts, CWG activities, and routine HPTN CORE study assessment.

Researchers must respond appropriately to potential gaps or limitations in the general literacy, health literacy or research literacy of research populations. While problems with general literacy may not interfere with obtaining meaningful consent, provisions to gain consent orally (with the potential involvement of a witness) should be in place to accommodate non- or semi-literate participants. In some communities, it may be necessary to hold pre-research discussions about general health and HIV/AIDS issues, such as routes of HIV transmission and the fact that asymptomatic HIV-positive persons can transmit the virus. Preparatory research literacy efforts may also be required to improve community understanding of culturally unfamiliar scientific concepts or study procedures.

Communicating the care components of research

Studies have indicated that some research participants believe erroneously that interventions conducted solely for research purposes are being implemented for their personal benefit. This phenomenon (generally termed the "therapeutic misconception" in trials involving therapies and more recently the "preventive misconception" for trials

involving prevention modalities) may reflect inadequate consent and underscores the importance of clearly communicating what are, and what are not, care components in the research. To facilitate this communication, HPTN site preparations for the implementation of specific research protocols need to ensure that these distinctions are clear. As a practical matter, this could include the construction of a table summarizing the elements of care provided to study participants that are

- part of the experimental aspects of the research project
- linked to non-testing aspects of research design, such as screening, and;
- purely to benefit the research participant

Such a table should also stipulate whether and for how long access to each element of care will be sustained at the end of research participation (see also Guidance Point 10).

This table would then be used as a guide when training staff about the risks and benefits of the research, and for describing research procedures, risks, and benefits in the informed consent process. The research should consider providing this supplemental information, once it has received appropriate regulatory review, during the informed consent process for new participants and at follow-up visits for participants already enrolled in the research.

Avoiding undue inducement

All research involves inducements, i.e. ways of motivating prospective research participants to join a study. Inducements are to be distinguished from reimbursements for travel costs, time away from work or child care costs. Undue inducements are inducements so attractive that they can cause research participants to join a study against their own best judgment and interests. What makes an inducement ‘undue’ depends on a number of contextual factors, including the risk involved in the study and the value an inducement may have in a particular context. To offer a substantial monetary inducement to an impoverished research participant to join a highly risky study may be exploitive and a violation of the ethical principle of respect for persons. Community consultation can be

invaluable for establishing appropriate inducements, given that a modest monetary inducement may be considered highly valuable in resource-poor settings. Investigators should inquire about inducements used in past similar studies, and any perceived issues with them. Concerns about possible undue inducement should not be used to rationalize overly modest inducements, thereby limiting remunerations to research participants. The inducements to be employed, their justification and the process of establishing their appropriateness should be specified in the study protocol.

Consent of non-research participants affected by research

In some HIV prevention research, non-research participants may be exposed to research-related risks, raising the question of whether their consent is required. For example, men may be exposed to physical risks from an experimental gel when their female partners participate in microbicide research. Explicit consideration should be given to the potential need to obtain consent from those affected by the research and whether it would be ethically appropriate to obtain specific consent. Relevant considerations include risks to those enrolled and not-enrolled as well as feasibility. Community engagement and local IRB review should facilitate deliberation about these issues.

Waiver of written consent and waiver of consent entirely

While it is preferable that the informed consent of the participant be recorded by the participant in some way (by signature or mark), circumstances may arise where respect for persons is better served by waiving this requirement and obtaining oral consent instead. In some settings, there may be deep cultural distrust about signing official documents. In some studies, the signature may be the only identifier linking the study with the participant, and waiving written consent may enhance confidentiality protections. Exceptions to written informed consent must take into account the potential risks of the study and ensure that the exception will not adversely affect the welfare and rights of research participants.

While obtaining informed consent is an ethical obligation for research involving human participants, in some cases it may be ethically justifiable not to seek and obtain consent.

Observational studies and some other types of 'not greater than minimal risk' studies may not require consent of participants under US government regulations and may be compatible with fundamental ethical principles. Discussions about waiving written consent, or waiving consent entirely, must be initiated among key stakeholders (particularly investigators, community representatives, and ethics review boards) early in the research design process.

Participation of children in research: assent and permission

Children, as defined in human rights documents, are persons below the age of 18 unless the age of majority is attained earlier according to local laws. Many children worldwide are exposed to HIV infection by means of perinatal transmission, breastfeeding, blood transfusion, sexual activity, sexual abuse or injection drug use. Since this population will be a primary target for decreasing HIV infection, particularly prior to sexual debut, it is important to involve children in HIV prevention research. Ethical conduct of HIV prevention research with children raises a number of significant challenges given physical and emotional immaturity, limited knowledge and relative lack of power in relations with adults.

Parental or guardian permission

The permission of parents or legal guardians is typically a prerequisite for the participation of children in research. Permission of one parent or legal guardian may be permitted if the host and sponsor ethics committees determine that the research poses minimal risk or where the child is likely to directly benefit from the research. Orphans and street children who are exposed to HIV infection may have no legal guardians and might therefore be automatically excluded from HIV prevention research if the requirement for parental or guardian permission is applied strictly. When a specific intervention stands to benefit orphans or street children, investigators should seek protective ways of including these groups in close consultation with community representatives, regulatory authorities, ethics committees, and local or national organizations devoted to the rights and welfare of children. The process of appointing

advocates for the participation of children in such circumstances should be consistent with US federal regulations (45 CFR 46.409).

In some jurisdictions, there are legal mechanisms permitting children to consent to research participation without the agreement or awareness of their parents or guardians. These mechanisms may include children who are married, have become parents, or live independently. In contrast, there may be local laws against sexual activity among younger adolescents which may bar them from entering into some trials. Researchers should conduct a thorough survey of local laws, in close collaboration with host-country experts, relevant to the inclusion of children in the early planning stages of research.

Assent

In United States federal regulations, assent is defined as "a child's affirmative agreement to participate in research." (45 CFR 46.402[b]). The host and sponsor ethics committees must determine whether children targeted by a study are capable of giving assent, and if so, whether the study protocol includes appropriate provisions for obtaining it. In general, investigators must respect a child's refusals to assent, even if parents have given permission. Where children are deemed incapable of giving assent, or where children stand to gain a benefit that is important to the health or well-being of the children and is available only within the context of research, ethics committees may waive the assent requirement.

HPTN researchers should be aware that in some countries, the requirement of obtaining assent is neither part of national law nor traditional medical practice. Formative research and community consultation should explore context-sensitive approaches to gaining assent from minors in research. Assent should be obtained from children according to their psychological and intellectual development, rather than any fixed age. In studies where children are HIV-positive but do not know their sero-status, conflicts arise between the requirement of assent and the disclosure of HIV status. In such cases, even if fully informed assent may not be appropriate, a gradual process of preparation for

disclosure involving parents/caregivers should be initiated in order to benefit the health of the child and protect others (Vaz and Corneli 2008).

Re-consent

Research is a dynamic activity conducted over time. Changes are often made to initial protocols, some of which may require re-consent of study participants. In general, these are changes in the research or in the circumstances of the participants. Changes in the research may include modifications of the purpose, potential risks and benefits, requirements of the research, or new information from other studies that may have implications for the research design or participants well-being. Changes in the circumstances of participants include, for example, consent of adolescents who have previously assented to participate in research but have gained the age of majority during the study. Women who become pregnant during the study may be candidates for re-consent, i.e. they must be informed of and agree to new potential risks and benefits to themselves and their fetuses.

General criteria for appropriateness of re-consent of research participants have been developed. Wendler and Rackoff (2002) distinguish between (a) material, significant changes and (b) material but non-significant changes, and different courses of action relative to each. Changes to the overall aims of research constitute a material and significant change, and require a full re-consent procedure. In cases of material but non-significant changes, mechanisms should be developed that inform study participants of modifications but fall short of full re-consent. For example, a slight increase in volume of a blood draw should not be considered sufficient grounds for re-consent since this would not significantly impact the welfare or rights of study participants. In such cases, researchers may orally disclose the changes to be made and seek oral agreement on the part of the participant, with documentation of the disclosure and agreement to the participant's study file. Such an approach should be agreed to by the ethics committees responsible for research review.

Particularly (but not exclusively) in longitudinal studies, the quality of the research participants' understanding may be compromised over time. This may be due to the

complexity of the study, uncorrected initial misunderstandings on the part of the participants, or rumors circulating in the local community. In studies where misunderstandings are foreseeable or already manifest in the behavior of participants, researchers should include on-going assessments of comprehension, correct misunderstandings on the part of participants, and respond to rumors in the community. If verbal or non-verbal indications of dissent or discomfort with participation are present, or expressions that indicate misunderstanding of the study, study staff should seek to identify and address the problem, resolve misunderstandings, and remind the participants that their involvement in the research is voluntary and they are free to withdraw.

Use of biospecimens

HIV prevention studies often involve the collection of human tissues, including blood, saliva, semen, or vaginal secretions. At a minimum, research participants should be given the information during the consent process regarding the use(s) of biospecimens collected from them including:

- Who will have access and control over the biospecimens
- Where the biospecimens will be analyzed and stored
- What uses will be made of the biospecimens in the current study
- What possible uses will be made of the biospecimens in future studies, and whether participants will be re-consented or be able to opt-out
- Whether the possible benefits of research on biospecimens are likely to be shared with participants or local communities
- Whether they will be informed of health conditions or health-relevant information (e.g., genetic vulnerabilities) that might be noted in analyses of biospecimens
- Whether their identifying information or links to their identifying information (i.e., codes) will be maintained with the biospecimens

Studies have indicated that local communities may be reluctant when it comes to collection, storage and analysis of human tissue, partly due to rumors about what is done with biospecimens when they are exported and analyzed in a distant locale or foreign country. Local research ethics boards should determine whether exportation of biospecimens in a particular study is necessary due to inadequate local laboratory or human resource capacity. HPTN investigators engaged in research involving the collection of biospecimens should, as part of general capacity building plans (Guidance Point 4), make reasonable efforts to contribute to local capacity in regard to storage and analyses of biospecimens. As part of community engagement (Guidance Point 3), HPTN investigators should involve local community representatives as early as possible in discussions about the use of biospecimens, and formative research is recommended to identify and appropriately respond to possible rumors and misconceptions surrounding collection of human tissue for research purposes. Whenever participants opt out of future uses of their biospecimens, HPTN should assist local researchers and institutions in efforts to retrieve and destroy biospecimens.

7. Addressing vulnerabilities

Guidance point 7: HPTN investigators should be aware of the social, cultural and other factors that may place research participants at heightened risk, and develop procedures and safeguards that appropriately monitor, assess and respond to these factors within the context of research.

Status: Ethical obligation

Responsible and accountable: Protocol team

For the purposes of this document, vulnerability is understood in terms of factors or conditions that place the health and well-being of individuals at heightened risk (including HIV exposure risk) in their daily lives as well as when they participate in HIV prevention research. Vulnerability has become a commonly used term in HIV-related

research and policy, and there is a wide range of diverse factors that contribute to vulnerability. These factors include: gender inequality; age or level of maturity; migration; stigmatization; discrimination; political oppression; criminalization; inadequate local health services; level of education, reproductive health education or education about HIV/AIDS; individual poverty; and political instability. HPTN researchers and other affiliated individuals are expected to be knowledgeable of the key vulnerability factors prevalent in the community where research is being conducted. It is beyond the scope of most research to rectify these factors, but knowledge of vulnerability factors should be translated into protections that ensure that research participation does not increase vulnerabilities and that vulnerabilities are not exploited in securing participation. For example, researchers may opt to conduct recruitment activities and study visits away from high traffic and visibility areas, such as clinics or hospitals.

Poverty

While poverty may not always raise risks of HIV exposure (given high HIV rates among some economically advantaged groups), lack of economic resources among research participants can nevertheless create ethical challenges within HIV prevention research. Some prospective participants may not be able to participate in a study due to inability to pay transportation costs. Some participants risk greater side-effects in certain drug trials partly due to inadequate nutrition. Those who engage in sex work may forgo elements of the standard of prevention package, such as using condoms, to ensure more income. In general, economically disadvantaged research participants will certainly have ancillary care needs. However, offering medical and other benefits and support to this population in order to address the vulnerabilities may run the risk of constituting undue inducement. Community representatives and ethics committees should be consulted on the most appropriate approach in specific cases.

Social inequality

When an individual is part of a group which has a low status in society -- such as injection and non-injection drug users, men who have sex with men, sex workers,

homeless individuals, illiterate persons, migrants or undocumented immigrants -- this can significantly affect whether and how that individual participates in HIV prevention research. Low social status may make certain groups hard to reach and this can pose significant challenges to recruitment and retention. Low social status may hinder the ability of individuals to make independent, autonomous decisions or make potential participants reluctant to join HIV prevention research. Given the high prevalence of gender inequality worldwide, and the feminization of the HIV epidemic globally, inclusion of women in HIV prevention research is both necessary and ethically challenging. Women may face practical obstacles to participation in research, given that women are disproportionally burdened with caring for children, the sick or the elderly. Women who participate in HIV prevention research may be viewed as 'HIV high risk' individuals, open to accusations of infidelity by their partners, and potentially subject to partner abuse. Recruitment of women into studies where they are required to use contraception may be difficult when a high cultural value is placed on fertility and child-bearing. The research team should take special care when making study-related contacts at women's homes or when providing study-related information to women, and make provisions for child care support and transportation, when appropriate.

Stigmatization

Some individuals (such as injection drug users, men who have sex with men, sex workers) engage in behaviors regarded by others as violations of moral, religious or legal norms, and which therefore are the object of strong disapproval by many sectors of society. Such individuals may be subject to police abuse, community humiliation or neglect by health care workers, and may face prejudice from social service or government agencies. They may also face stigma in their own families. Recruitment of such individuals in HIV prevention research may, if they are thereby identified as 'at risk for HIV', increase stigmatization and potential harm. When recruiting from known stigmatized groups, researchers should integrate a stigma-reduction plan into their research. Elements of such a plan might include: a review of successful evidence-based approaches to stigma reduction, information gathering to identify forms of stigma prevalent in the community (such as physical exclusion of individuals from family

homes, inability to obtain visas or scholarships, or common denigrating labels placed on persons living with HIV/AIDS) by means of preliminary social science research; collection and analysis of social harms data and integration of findings into study SOPs; raising stigma awareness among fellow researchers and those involved in research implementation such as local clinicians, nurses and field workers; being mindful of the use of language (especially in local translation) to describe the study and study population in recruitment documents, consent forms and fact sheets; ensuring that the study's community representative is supportive of stigmatized populations and that community engagement activities are partly devoted to stigma reduction; ensuring that the research environment constitutes a private and confidential 'safe space' where participants can share their personal experiences and concerns.

Challenges to protecting vulnerable populations in research

Injection drug users (IDUs) are stigmatized to such a great extent that it is very difficult to provide traditional research protections for IDUs who enroll in HIV prevention research. IDUs are often regarded by local governments, local police authorities and many community members as common criminals, and research involving them tends to be discouraged. When research does occur, the government closely monitors who the IDUs are and the local police, who have all the names of participants may watch them coming in and out of the clinic. In this political and social context, the idea of providing true confidentiality protections for these research participants does not apply, so researchers are forced to look to other risk-reduction approaches for this population. This can involve educating police about proposed research in order to minimize risk to participants.

Discrimination

People living with HIV in some settings may enjoy the same rights, protections and social benefits as fellow, non-HIV positive citizens. In some countries, however, those known to have HIV may face obstacles gaining or retaining employment, medical care or legal representation. When a person participates in a primary HIV-prevention research study, they may be considered HIV positive and for that reason they may face

discrimination similar to that faced by HIV-positive persons in their community. Researchers should explore ways of minimizing potential discrimination due to participation in HIV prevention research by joining efforts and sharing information with local human rights groups and civil society organizations dedicated to protecting persons living with HIV/AIDS. If feasible, the confidentiality and privacy protections for research participants should be developed in consultation with such groups and organizations, and incorporated into the research protocol, site preparation, and SOPs as appropriate.

When involving research participants subject to the above described (or other) vulnerability factors, investigators should devote special care to recruitment and retention activities in order to minimize potential research-related harms. The investigator should engage community groups to share information, raise awareness and address community concerns before study participants are recruited.

8. Ethical review of research

Guidance point 8: HPTN research protocols will be reviewed by independent ethics review boards in the host country. HPTN should encourage capacity-building of host country ethics review where appropriate.

Status: Ethical obligation

Responsible and accountable: Sponsor, HPTN CORE operations, site Principal Investigator

International ethics guidance documents agree on the need for independent ethical review of research protocols, but differ on the requirement that research protocols be submitted to ethical review in the localities where research will be conducted. The current Declaration of Helsinki (2008) and the CIOMS guidelines (2002) state that research protocols should be reviewed by an independent ethical body, but do not specify local review. The UNAIDS *Ethical considerations in biomedical HIV prevention trials*

(UNAIDS 2007a) states categorically that it is unethical to conduct HIV prevention research if there is not adequate local review, even if the protocol has been reviewed and approved elsewhere. Where a local ethics body exists but has limited capacity, initiatives should be taken to sufficiently strengthen ethics review capacity. Given possible conflicts of interest when researchers themselves help strengthen ethics boards who may review their studies, it is recommended that the study sponsor, the HPTN Core and other agencies be involved in these capacity-building efforts.

HPTN has always obtained the approval of a local ethics review body, in both international and US domestic settings, before conducting its research. Local research ethics committees can have a better appreciation of study-related risks and benefits against the background of cultural norms and social realities. The HPTN reiterates its commitment to obtaining local ethics approval wherever it conducts its research. These ethical review boards should possess basic characteristics as stipulated in US and international documents, such as independence, gender and disciplinary diversity of reviewers, and inclusion of non-institutional members. In some cases, however, such as multi-site studies among similar populations, it may however be advisable to not to have ethics review at each site in order to avoid duplicative procedures and excessive bureaucratic burdens.

In international research, the regulations used by local research ethics committees are often not, and need not be, identical to US federal regulations. Potential conflicts between judgments of sponsor and host research ethics committees should be handled by designated HPTN investigators and staff members cognizant of the regulations and approaches employed by these bodies.

Section II: Ethical issues during the conduct of research

9. Standard of prevention

Guidance point 9: In partnership with key stakeholders, HPTN should establish a package of effective, comprehensive and locally sustainable prevention services to be offered to participants in each HPTN study.

Status: Ethical obligation (provision of prevention package) and ethical aspiration (content of prevention package)
Responsible and accountable: Protocol team

The principle of beneficence obligates investigators and sponsors to minimize risks to participants in HIV prevention trials. Participants must be provided with effective means to minimize their risk of acquiring HIV during the course of the research. These means are sometimes referred to as the "prevention package". Nevertheless, it can be practically and ethically challenging to determine the content of the prevention package. While some guidance indicates that the prevention package should include appropriate counseling and all 'state of the art' HIV risk reduction methods (UNAIDS 2007a), this may be infeasible in practice. For example, some prevention methods, such as male circumcision, may be considered inappropriate in communities where there are strong religious and cultural objections to it. In some countries, it may be illegal to provide certain prevention methods which have been shown effective, such as needle exchange. In addition, offering an extensive array of HIV prevention methods when these methods are not generally available in the community may also constitute undue inducement to participate and/or create strong inequities between study participants and non-participants.

HPTN's approach to the standard of prevention is pragmatic and context-sensitive, but also aspirational. The necessary conditions for an acceptable prevention package within HPTN research projects are that components are 1) known to be effective means of prevention for HIV transmission; 2) practically achievable as a standard in the local setting; and 3) are reasonably accessible by those who are screened or enrolled.

Effective means of prevention refers to those interventions for which good evidence of effectiveness exists and for which there is no reasonable basis for questioning the effectiveness of the method in the local research setting. HPTN investigators have a responsibility to keep current with new information and developments in HIV prevention research that may be relevant to the standard of prevention in a given HPTN trial, and make modifications where appropriate.

Reasonably accessible indicates that the services are free or at a cost within the means of research participants, can be implemented safely and legally within the research participants' community, and that, if no other significant obstacles to access exist, they can be reasonably overcome by efforts of investigators and the CAB. In general, services may be provided through referral if the referring clinic meets these criteria for accessibility, if direct provision of the services would critically overwhelm the capacity of the research staff, or if the service requires expertise or specialized skills that go beyond what is reasonably necessary for implementation of the trial.

Practically achievable means the services could reasonably be implemented and sustained in the community independent of the resources and infrastructure required for the conduct of the clinical trial. This does not preclude the possibility of improving on the existing local standard of care but it does require such improvements will be on a par with the requirements of the trial, e.g. laboratory procedures needed for the confirmation of outcome measures. Additionally, such services should not undermine other existing services in the community, e.g. by requiring that limited resources be shifted to provide the new services.

Although these conditions are necessary in determining the standard of prevention, they are not sufficient to warrant inclusion. The HPTN's 'aspirational but pragmatic' approach to determining the ethically appropriate standard of prevention is driven both by the principle beneficence as well as social justice. The standard of prevention within the research should not be so radically superior to the current standard of prevention in the surrounding community that it could not be feasibly integrated into local health care

services in a reasonably timely manner after research is over. Requiring all 'state of the art' prevention services within HIV prevention research would (besides potentially compromising the real-world significance of the data) create serious inequities between research participants and community members with similar needs. In addition, providing a 'state of the art' prevention package to a control arm could compromise the ability of a study to prove that a new prevention method is significantly better (or worse) than the current standard of prevention in the surrounding community, and therefore could hinder the development of a potentially more effective and sustainable prevention approach.

As a minimal package, every HPTN research protocol will explicitly consider the need for HIV voluntary counseling and testing, HIV and STI risk reduction counseling (including counseling to reduce risks related to substance use) and male and female condoms provided to research participants. Beyond this, each site and protocol team may identify additional services to be provided to expand beyond this minimum. Use of sterile needles and syringes, or promotion of male circumcision, have been shown effective, but may be illegal or culturally inappropriate as part of the prevention package in some settings. Should an HPTN protocol team or HPTN site implementing a protocol believe that provision of a known method of prevention would be considered inappropriate and, therefore, may not be feasible in a local research setting, this must be communicated to the chair of the respective protocol team and the EC along with supporting evidence. Concurrence by the protocol chair and EC in deciding to not offer a proven HIV prevention method at a local research site must be obtained.

In regard to inclusion of previously tested interventions into the standard of prevention in subsequent research, by way of example, a series of randomized controlled trials have indicated that male circumcision is an effective means of reducing men's risk of acquiring HIV from heterosexual intercourse. This raises the question of whether the design of current and future HIV prevention studies ought to include male circumcision as part of the 'prevention package'. To respond to this question, distinctions should be made between possible obligations:

- to provide information about the known effectiveness of clinically-performed male circumcision to reduce risk of HIV acquisition
- to actively promote male circumcision as part of the counseling process
- to provide referral mechanisms to male circumcision services in the local health care system, and
- to provide circumcision services as part of the research protocol

Obligations will depend on the state of local health services and the outcome of community engagement and consultation on this issue. When there are no local safe, clinical male circumcision services to which the participants could have access, participants should still be informed about the efficaciousness of the intervention and the issue should be part of community education initiatives. Provision of circumcision services as part of the research 'prevention package' is controversial. There are issues of cost, cultural acceptability, and the potential to create privileged access to circumcision services by research participants. As with other prevention modalities which are not 100% effective, there may be the potential for behavioral disinhibition, which could undermine other preventive efforts. HPTN should consult with community members and stakeholders to seek the most feasible and appropriate way of previously tested interventions into HIV prevention research designs.

This view of the standard of prevention acknowledges that there is a continuum of prevention services, and what is actually provided may differ between countries, regions, or clinics implementing the same research protocol. At the same time, the prevention package in HPTN research projects (particularly in a control arm) should not replicate sub-standard prevention services in the community, and it is desirable for HPTN and other stakeholders to serve as resources to host-country advocates seeking to modify local laws that prohibit the use of evidence-based prevention methods, such as the exchange of sterile injection needles. If the standard of prevention within a study is predicated on the lack of local resources or questionable policies and legislation, HPTN must carefully consider whether the research reproduces or reinforces an inadequate and modifiable status quo, or alternatively, whether it can be justified by its potential to convincingly

demonstrate the superior impact of a new preventive approach in comparison to current community standards of prevention. HPTN should engage in strong advocacy for improved prevention programs in the community before or in tandem with investing resources in the testing of alternative intervention methods.

Consistent with Guidance Point 4 (Building Local Capacity and Partnerships), the each research site investigator should identify what prevention services are available to the local community and whether (and to what extent) the prevention package offered in the research exceeds the local prevention standard of care. Because the provision of prevention services in the local community may change over the course of a trial, local investigators may need to periodically reassess local standards compared to the prevention package offered by the research. The protocol team may need to re-address concerns about undue inducement and dual standards of prevention in partnership with key stakeholders as the trial continues and local standards change.

10. *Standards of care and treatment*

Guidance point 10: In designing the care and treatment package to be provided to study participants, HPTN will meet and strive to exceed local standards of medical services, while taking into account the implications of those standards for research participants, and the potential impact that research-associated care may have on local communities.

Status: Ethical obligation (establishing standards of care and treatment) and ethical aspiration (content of standards)
Responsible and accountable: Site Principal Investigator, protocol team

Standards of prevention refer to what research participants may or may not receive to lower their risk of HIV infection. Standards of care and treatment refer to the package of services the research participant can expect to receive in terms of medical care or treatment. HPTN researchers must be knowledgeable of the current standards of care in the local community, provide at the very least equally adequate care services, and seek to enhance standards of care both within and outside the research study especially if local standards are extremely low.

There are different domains of care to be considered:

- Care and treatment for those screened but failing to meet study inclusion criteria due to a medical condition (such as HIV infection)
- Care and treatment provided to participants for study-related reasons
- Care and treatment provided to participants for medically significant findings occurring during study participation ('ancillary care')
- Care, treatment and/or monetary compensation for research-related injuries

Care and treatment for those screened out

Screening procedures for HIV prevention research sometimes identify previously undetected medical conditions of prospective research participants. Richardson (2007) offers a framework to evaluate the stringency of researcher obligations to provide care in

such cases. According to this framework, the degree to which researchers are obligated to provide care depend on five factors: (1) participants' vulnerability (how badly off they would be if they did not receive help) (2) participants' degree of dependence on the researchers (whether they lack other sources of possible help) (3) participants' uncompensated risks or burdens (4) the expected depth (intensity and duration) of the researcher-participant relationship and (5) the cost to the researchers (in money, personnel or study power) of providing the relevant care.

Applied to the case of care and treatment for those testing HIV-positive at screening, the strength of obligations depends on local conditions. On the one hand, researchers are unlikely to have a long or intense long relationship with those screened out, and the costs of providing antiretroviral treatment for every HIV-positive person excluded (particularly in high HIV prevalence settings) could be substantial. On the other hand, those screened out may need antiretroviral treatment and have no alternative means of access. Before research begins, local investigators must address these situations proactively through capacity-building, information-gathering, and meetings with key stakeholders, particularly representatives of health ministries and local health institutions, to decide upon equitable and sustainable solutions.

Care and treatment provided for study-related reasons

The package of care and treatment that participants can expect as part of their involvement should be clearly expressed in the study protocol and accurately reflected in the consent process. Depending on the type of research, study population, setting and consensus reached by investigators, sponsors and other key stakeholders, this may include:

- Treatment for STIs
- Nutrition and/or nutritional advice
- Family planning
- Reproductive health care for pregnancy and childbirth
- Psychosocial support or referrals to such support

- Palliative care
- Home based care
- Antiretroviral treatment

There is a growing consensus that those who become HIV-infected in an HIV-prevention trial, and whose need has been clinically established, have a right to receive care. There are different possible ways to defend such a right. According to the framework described by Richardson (2007), such participants typically have a long-standing relationship with researchers and given that there are commonly relatively few participants who seroconvert, even in phase III trials, the costs of treatment provision could be modest. Some argue these participants should, as a matter of reciprocal justice, get treatment in return for having become HIV-positive. Others argue that treatment should be provided to avoid ethical double standards, because participants in HIV prevention trials in developed countries routinely have access to antiretroviral treatment.

Whether such reasons add up to an ethical obligation is a matter of continuing debate. Investigators, research sponsors, local governments and international agencies should strive to provide access to antiretroviral treatment for those who seroconvert during HPTN trials, albeit in ways that do not worsen in-country inequalities. Conducting HPTN research in locations when provision of antiretroviral treatment to seroconverters is not feasible or guaranteed may be permissible if host governments and communities are committed to the research and if the capacity-building plan includes improvement of local HIV/AIDS services and care.

Ancillary care

Ancillary care can be defined as health-related care services provided to research participants which are not required to make a study scientifically valid, ensure a study's safety, or compensate for research-related injuries. Monitoring drug interactions or providing care for adverse reactions to a study drug are not ancillary care. By contrast, following up on diagnoses found by study tests but are unrelated to the study's aims

would be ancillary care. Provision of ancillary care may reinforce trust between researchers and communities, but can also increase inequities in health care access.

Questions about ancillary care tend to arise frequently in conduct of research in low-income settings with weak health care infrastructures. It is recommended that pre-research community consultation and systematic assessments be conducted to reveal some of the prevalent health conditions in the local population in order for investigators to anticipate at least some of the ancillary care needs of study participants. Some of these needs will emerge during the implementation of research itself. Which of these needs should be attended to, and which not, depends on a variety of factors, such as those indicated in the framework mentioned above (Richardson 2007). The exact nature of the decision-making process that weighs these factors cannot be prescribed. Each research protocol and local context may present unique challenges. However, the process should include opportunities for open dialogue by key stakeholders, clarity about the ethical question to be addressed, and commitment to reaching a timely decision. It would be desirable to develop strategies for enhancing the efficiency of this decision-reaching process. The HPTN Executive Committee, CWG, and EWG should discuss and, where feasible, establish generally-agreed upon (*prima facie*) standards for the provision of care during all HPTN research. If developed, such standards should be periodically reviewed with reference to new data, consensus statements, and recommendations regarding care, and revised if substantively warranted and appropriate.

Compensation for research-related harm

International guidance documents, as well as some national guidelines, recommend or require that participants receive compensation for research-related injuries (cf. CIOMS Article 19; Medical Research Involving Human Subjects Act). In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health. However, compensation for injury can be handled at the site level by arrangements with institutions conducting the research. In some cases, NIH funds can be used to purchase insurance to cover compensation for injury, when national regulations in the host country require that this provision be in place. When compensation

for injuries will not be offered, this must be stated explicitly in the consent process. When compensation will be offered, the consent process should describe the nature of the compensation available to research participants for harms that may occur during the conduct of the study. The information provided should, incorporating considerations from relevant legal codes, distinguish between negligent and non-negligent harm, the medical treatment to be provided for injuries incurred, possible monetary compensation for lost income, and the process by which harms are determined to be research-related and compensated. The consent process should include information about possible compensation for social and economic harms attributable to research participation in addition to physical harms. HIV infection acquired during a HIV prevention study should not be considered a research-related harm unless it can be established that the infection is directly due to the study product or research-related activities.

11. Independent data safety and monitoring

Guidance point 11: Particularly in late-stage clinical trials, HPTN should ensure that an independent data monitoring committee is in place in order to help ensure study validity and safety, and assess whether it would be in the interest of study participants to modify or terminate a study. Reliable mechanisms should be established to communicate the results of this independent review to key stakeholders.

Status: Ethical obligation (for late-stage studies)

Responsible and accountable: Sponsors

Data Monitoring Committees or Data Safety and Monitoring Boards (DSMB) are advisory committees used especially in late-stage, multi-site clinical trials involving significant risk. The DSMB typically reviews unblinded data on safety and efficacy. As such, it stands in a position to determine whether harm or benefit due to the study intervention is occurring or whether a clinical trial cannot achieve informative results if it continued ("futility") and may recommend modifications or stopping the trial as appropriate. The DSMB has an ethical and scientific mandate to ensure the continuing safety of research participants and the ongoing validity and scientific merit of the

research. The DSMB is meant to operate independently of the trial's sponsors and has a number of key functions:

- Internal and external study monitoring to ensure data validity, including reassessment of assumptions underlying sample size calculations and study duration
- Determining whether interim analyses justify early termination of the study for reasons of futility or loss of clinical equipoise
- Assessing emerging unanticipated safety issues, such as a significant number of serious unexpected adverse events that may be intervention-related
- Evaluating external information from other studies that may necessitate modification or termination of the study being monitored

According to NIH policy, a DSMB is required for all multicenter Phase III trials. The Division of AIDS (DAIDS) monitors safety and efficacy of multicenter randomized clinical trials through standing DSMBs, rather than establishing boards for each new trial. Membership on the DSMB reflects the disciplines and medical specialties necessary to interpret the data from the trials it reviews. This includes biostatisticians, medical ethicists, regional and community representatives, and clinicians knowledgeable about the diagnosis and treatment of the diseases under study.

When a study includes a DSMB, a communication plan should include preparations for handling information from DSMB reviews. The communication plan should detail how information and recommendations from the DSMB will be shared internally among research team members, as well as externally among ethics review committees, research participants and communities, when appropriate. According to US Federal regulations (45 CFR 46), Institutional Review Boards have are responsible for monitoring ongoing research with human subjects. Consequently, responsible local ethics review committees should be notified of the outcome of all DSMB reviews, even if no major changes are recommended, in order to document that data and safety monitoring is occurring as expected. When early termination occurs or if there are major modifications

recommended by a DSMB, these findings should also be reported in a comprehensible and timely way to local ethics committees and communities hosting the research. In some cases, such as the early termination of male circumcision trials, the DSMB may recommend to unblind interim results of a study to investigators and participants when doing so is believed to be in the best interests of study participants. The DSMB should also provide concrete recommendations when a termination occurs, such as provision of a beneficial intervention to the control arm of the study.

Section III: Ethical issues after data collection is completed

12. Dissemination of research results

Guidance point 12: HPTN will plan for the timely communication and dissemination of HIV prevention research results to participants, research staff, local communities and other audiences in a manner that promotes comprehension and trust.

Status: Ethical obligation

Responsible and accountable: Protocol team, sponsor, network leadership

The obligation to disseminate research results expresses the values of respect for persons and communities. Study participants and communities are entitled to know the results, in a timely matter, of the research their involvement made possible. Both positive and negative results should be publicly available, and communicated in accessible ways, according to the targeted audience, using a variety of media in addition to academic publications (such as community meetings, theater pieces, community radio, CAB newsletters, newspapers or television programs) where appropriate. The dissemination of

results should be part of a comprehensive communication plan (particularly for large multi-site phase II/III trials) that conveys how a tested efficacious intervention will fit with and strengthen existing HIV prevention strategies, and how it can be regarded as an opportunity to reinforce HIV prevention messages and combat possible rumors and concerns. Particular attention should be focused on devising messages that minimize behavioral disinhibition. The protocol team should include plans for dissemination of research results in the study protocol, and community advisory board input is crucial in developing an effective communication plan. Communication of research results must protect the confidentiality of individual participants, and where appropriate, communities in which the research was conducted.

13. Sustaining capacity-building and infrastructure into the future

Guidance point 13: HPTN will work to increase the likelihood that the investments made in capacity-building and infrastructure will continue to provide benefits and opportunities for local communities after the research is over.

Status: Ethical aspiration

Responsible and accountable: HPTN

The capacity built in the course of designing and implementing HPTN research (see Guidance Point 3) should ideally contribute to future research activities and public health, and in that way provide a foundation for ongoing benefits to the local community once the research is completed. Investigators have a responsibility to explore, together with local partners, various means of sustaining and strengthening the improvements to local capacity, including collaborative grant-writing initiatives, institutional agreements, staff training, publication activities, scientific exchanges, student training, and research and ethics education projects for communities. Approaches for sustaining capacity and infrastructure after research is over should be outlined in the study protocol or made into a plan separate from the protocol. These should be modified in the light of updated

assessments of local needs in close partnership with community representatives. Partners should also help to ensure that the capacity and infrastructure that has been developed will be sustained and utilized responsibly, i.e., in ways that will directly or indirectly benefit the health of local communities.

14. Continuing care for research participants

Guidance point 14: HPTN research projects must make reasonable efforts to ensure continuity of care after termination of research, where appropriate, for participants who have received (and continue to need) medical care and treatment during their involvement in HPTN research.

Status: Ethical aspiration.

Responsible and accountable: Site principal investigator

This guidance point concerns post-study continuation of care and treatment services, as distinguished from provision of tested effective interventions (Guidance Point 15). It is contrary to the principles of respect for persons and beneficence that needed and effective interventions beneficial to a person's health be withdrawn. Caution should be taken to accurately convey the true likelihood of continuity of care to participants. As stated in Guidance Point 10, different types of care may be included in the package of services offered to research participants, who may still need some components of the package after the research is completed. They may also still be in need of ancillary care or care provided as a result of research-related harm. While investigators should ensure that there is no discontinuity of care and treatment for study participants, research studies are not a substitute for local health care systems, and therefore continued care and treatment should ultimately be provided by local health services. At a minimum, investigators are responsible for referrals to local services that provide an acceptable level of care. When no adequate referrals currently exist, investigators should work together with local health authorities to try to build local capacity (see Guidance Points 3 and 4). If the development of an adequate referral system is not feasible, despite capacity-building efforts, researchers should consider alternative study sites. The formation of long-term

partnerships with local institutions is crucial to developing standards of care within research itself and for the continuity of care after research is over. The *Partnering for Care* project has identified seven steps in developing systems of care related to HIV research (McQueen and May 2008):

1. Build a public health attitude among research leaders and staff
2. Assess the local community's values, attitudes, and priorities
3. Assess assets and constraints of the public-health system
4. Engage the community
5. Determine the extent of care to provide, and the balance between direct versus indirect care
6. Build relationships with nearby resources
7. Develop a referral system

What care is provided and for how long can only be answered on a case-by-case basis. The investigator should consider factors like the evolving availability of the care in the community and the foreseeable health impact (on individual and public health levels) of disrupted care and weigh this against potential for creating inequitable access to health care services because of research participation. Information related to continuing care should be communicated to study participants through various media, such as study websites or bulletin boards. In addition, efforts should be made to develop a follow-up and monitoring system to ensure that the referral system in fact provides adequate health services.

Continuity of care and evolving standards of care

The protocol of HPTN 052 stated that during its five-year study period every HIV positive research participant would receive study-provided antiretroviral treatment (ART), either upon randomization or when their CD4 cell count falls to a certain threshold. When the protocol was finalized the sponsor, DAIDS, asked each site to provide a letter outlining whether or not the participants at their site would have access to ART upon study completion. The information in these letters was then incorporated into the site-specific consent forms. In Brazil, where ART is provided free from the government, the letter and consent form stated that every participant would have access to government-provided ART at the end of the study. Some sites however, such as those in India, would not guarantee ART at the end of the study, but they did promise that the participants would be informed of other studies, which could potentially provide them with free ART. Since these letters and consent forms were originally developed, several countries - including Malawi, India, and Thailand - have begun government-sponsored ART access programs - so the majority of the participants in HPTN 052 will have access to free ART upon study completion. At the beginning, many investigators felt that the benefit of having access to free ART for 5 years outweighed the risk of not knowing whether access to ART would be available after that period. In short, the ethical issue of access to ART after study completion has eased as more and more countries have begun government-sponsored programs that provide free ART to all that need it.

15. Provision of successful research interventions

Guidance point 15: HPTN research seeking to establish the efficacy of an intervention must have a preliminary plan regarding the provision of successful interventions to research participants and communities.

Status: Ethical obligation (plans regarding the provision of successful interventions to participants) and ethical aspiration (provision of successful interventions to participants, communities and at-risk populations)

Responsible and accountable: Sponsor, site PIs, local partners, protocol team

The Declaration of Helsinki (2008) states that study participants are entitled to share any benefits that issue from research, including interventions identified as beneficial, at the conclusion of the study. The position stems from considerations of social justice, i.e., that those who carry the burdens of research should also enjoy its benefits. However, research may produce different kinds of beneficial interventions, and immediate provision may not always be feasible. Male circumcision was immediately offered to participants in the non-intervention arm after the protective benefit of the intervention was established (Auvert 2005;Gray 2007; Bailey 2007). However, drug interventions may require regulatory approval and production scale up before they can be provided. Moreover, in many studies, the results may not be definitive or the benefits may not be of great clinical significance. For these and other practical considerations, obligating researchers to provide access to all beneficial interventions at the conclusion of research is not reasonable. However, researchers are required to create an explicit preliminary post-study access plan, which need not form part of the research protocol. While it may be unreasonable to expect conclusive definition of these arrangements before the intervention has been tested, this plan should nevertheless be developed in early planning stages and refined as research evolves.

In plans for post-study access, a number of questions must be addressed:

- *Who will be financially and logistically responsible for providing the intervention*. Typically, this responsibility will not fall to any one institution or agency involved in or affected by the research. Where appropriate, stakeholders should explore the creation of pooled funds for this purpose.

- *To whom access will be provided: study participants, their communities or others.* Consultations must address questions of cost and equity. The wider the access, the larger the financial implications; the narrower the access, the greater risk of inequity between research and non-research participants. Support from local health institutions to incorporate the intervention into routine practice may ease the tensions between cost and equity. Researchers should, in partnership with

local institutions, advocate for widest practicable access to interventions beneficial to local communities and populations at risk for HIV.

- *How long access will be provided*. Provision of free, life-long access to interventions to research participants, if applicable, raises issues of equity. The provision of life-long access may not be appropriate in some cases, e.g., if long-term efficacy is unproven or long-term side effects are unknown.

When an HIV prevention intervention proves efficacious, study participants may want to continue using the product after the research is over. There may be significant barriers to continued access, such as cost, availability, and regulatory review before the product is officially licensed for use. The protocol team should anticipate issues of continued access in late-stage study protocols, and relevant information should be conveyed to prospective participants during the consent process. Creative solutions should be explored to avoid regulatory obstacles to access of new and efficacious prevention approaches, such as unblinding a prevention study, providing those in the control arm access to the study product (and continued access to those in the active arm), and changing the study into a long-term safety trial.

Concluding note

HPTN has the mission of conducting HIV prevention research at the highest scientific and ethical standards. This ethics guidance document expresses the fundamental ethical principles to which HPTN subscribes, and specifies the ethical obligations and aspirations of HPTN and its stakeholders in regard to the conduct of HIV prevention research. This document will be revisited and likely revised in response to new developments in HIV prevention research and evolving ethical debates. HPTN CORE/EC has the responsibility to disseminate this document to those involved in HPTN research and to ensure that its considerations are incorporated into research protocols and scientific conduct in the field.

Bibliography

Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. (2005) Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial. PLoS Med. Nov;2(11):e298.

Bailey RC, Moses S, Parker CB, et al. (2007) Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomized controlled trial. *Lancet.* 369, 643-56.

Cohen MS, Kaleebu P, Coates T (2008) Prevention of the sexual transmission of HIV-1: preparing for success. *J Int AIDS Soc* 11(1): 4. Available at: http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2584059&blobtype=pdf.

Collins C (2005). Gaps and inconsistencies in ethical guidance for HIV prevention research. Geneva: Joint United Nations Programme on HIV/AIDS. Available at: http://ews.unaids.org/public/CreatingeffectivepartnershipsforHIVPrevention/Documents/.

Corneli AL, Bentley ME, Sorenson JR, Henderson GE, van der Horst C. (2006) Using Formative Research to Develop A Context-Specific Approach to Informed Consent for Clinical Trials. *Journal of Empirical Research on Human Research Ethics* 1(4): 45-60.

Delor F, Hubert M (2000) Revisiting the concept of vulnerability. *Social Science and Medicine* 50: 1557-70.

Ethical considerations related to the provision of care and treatment in vaccine trials. Meeting report. (2007) *Vaccine* 25: 4863-4874.

Global Campaign for Microbicides (2005) Rethinking the ethical roadmap for clinical testing of microbicides. Report on an international consultation. Available at: http://www.global-campaign.org/researchethics.htm.

Global HIV Prevention Working Group (2006). New approaches to HIV prevention: accelerating research and ensuring future access. Menlo Park, California. Available at: http://www.paho.org/English/AD/FCH/AI/New%20Approaches%20to%20HIV%20Prevention.pdf.

Gray RH, Kigozi G, Serwadda D, et al. (2007) Male circumcision for HIV prevention in men in Rakai, Uganda: a randomized trial. *Lancet*. 369, 657-66.

Hicks L, Laupacis A, Slutsky AS (2007) A primer on data safety monitoring boards: mission, methods, and controversies. *Intensive Care Medicine* 33: 1815-1818.

Institute of Medicine (2008) Lagakos SW, Gable AR (eds.) Methodological Challenges in Biomedical HIV Prevention Trials. National Academy of Sciences.

Institute of Medicine (2007) PEPFAR implementation: progress and promise. National Academy of Sciences. Available at: http://www.iom.edu/CMS/3783/24770/41804.aspx.

Lange JMA (2005) We must not let protestors derail trials of pre-exposure prophylaxis for HIV. *PLoS Med* 2(9): e248.

Lie RK, Emanuel EJ, Grady C. (2006) Circumcision and HIV prevention research: an ethical analysis. *Lancet* 368 (9534): 522-5.

Lo B, Padian N, Barnes M (2007) The obligation to provide antiretroviral treatment in HIV prevention trials. *AIDS* 21: 1229-1231.

London A, Kimmelman J (2008) Justice in translation: from bench to bedside in the developing world. *Lancet* 372 (9632): 82-85.

Macklin R (2008) Standard of care: an evolution in ethical thinking. *Lancet* 372: 284-285.

MacQueen KM**,** Alleman P. International perspectives on the collection, storage, and testing of human biospecimens in HIV research. *IRB: Ethics & Human Research* 2008; 30(4):9-14.

MacQueen KM, Namey E, Chilongozi DA, Mtweve SP, Mlingo M, Morar N, Reid C, Ristow A, Sahay S, HPTN 035 Standard of Care Assessment Team (2007) Community perspectives on care options for HIV prevention trial participants. *AIDS Care* 19(4): 554-560.

MacQueen KM, Sugarman J. (2003) HIV Prevention Trials Network. Ethics Guidance for Research. April 15, 2003. Available at: http://www.hptn.org/Web%20Documents/EWG/HPTNEthicsGuidanceFINAL15April2003.pdf.

MacQueen KM, Karim QA (2007) Practice brief: Adolescents and HIV clinical trials: ethics, culture and context. *Journal of the Association of Nurses in AIDS care* 18(2): 78-82.

MacQueen KM, May M (2008). Partnering for care in HIV prevention trials. A how-to manual. Family Health International. Available at: http://www.fhi.org/en/RH/Pubs/booksReports/Partnering_for_Care.htm.

Milford C, Wassenaar D, Slack C (2006). Resources and needs of research ethics committees in Africa: preparations for HIV vaccine trials. *IRB: Ethics and Human Research* 28(2): 1-9.

Mills E, Nixon S, Singh S, Dolma S, Nayyar A, Kapoor S (2006). Enrolling Women into HIV preventive vaccine trials: an ethical imperative but a logistical challenge. *PLoS Med* 3(3): e94.

Mills EJ, Singh S, Singh JA, Orbinski JJ, Warren M, Upshur RE (2005) Designing research in vulnerable populations: lessons from HIV prevention trials that stopped early. *BMJ* 331: 1403-1406.

Moodley K (2007) Microbicide research in developing countries: have we given the ethical concerns due consideration? *BMC Medical Ethics* 8(10). Available at: http://www.biomedcentral.com/1472-6939/8/10.

Muula AS, Mfutso-Bengo JM (2007) Responsibilities and obligations of using human research speciments transported across national boundaries. *J Med Ethics* 33: 35-38.

NIAID (2006) Charter for the data and safety monitoring boards of the Division of AIDS. National Institute of Allergy and Infectious Diseases. Available at: http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/DSMB_Charter.pdf .

NIMH Collaborative HIV/STD Prevention Trial Group (2007) Ethical issues in the NIHM collaborative HIV/STD prevention trial. *AIDS* 21 (suppl 2): S69-80.

NIMH Collaborative HIV/STD Prevention Trial Group (2007) Role of the data safety and monitoring board in an international trial. *AIDS* 21 (suppl 2): S99-102.

Nuffield Council on Bioethics (2005). The ethics of research related to health care in developing countries. A follow-up discussion paper. Available at: http://www.nuffieldbioethics.org/go/ourwork/developingcountries/introduction.

Padian et. al. (2007) Diaphragm and lubricant gel for prevention of HIV acquisition in south African women : a randomized controlled trial. Lancet 370 (9583): 251-261.

Participants in the 2001 Conference on ethical aspects of research in developing countries. Fair benefits for research in developing countries. *Science* 2002 298 (5601): 2133-4.

Participants in the 2006 Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries (2008). The Ancillary-Care Obligations of Medical Researchers Working in Developing Countries. *PLoS Med* 5(5): e90.

Participants in the 6th Global Forum on Bioethics in Research (2005) What happens when research is over? Post-trial responsibilities of researchers and sponsors. Summary of feedback from delegates. Available at: http://www.wellcome.ac.uk/stellent/groups/corporatesite/@msh_grants/documents/web_document/wtx027291.pdf.

Rennie S, Muula AS, Westreich D. (2007) Male circumcision and HIV prevention: ethical, medical and public health tradeoffs in low-income countries. *J Med Ethics* 33(6): 357-61.

Resnik D and Sharp R. (2006) Protecting third parties in human subjects research. *IRB* 28, 4: 1-7.

Richardson HS, Belsky L (2004) The ancillary care responsibilities of medical researchers. *Hastings Center Report*, January-February: 25-33.

Richardson HS (2007) Gradations of researchers' obligations to provide ancillary care for HIV/AIDS in developing countries. *AJPH* 97(11): 1956-61.

Schuklenk U, Ashcroft R (2007) HIV vaccine trials: reconsidering the therapeutic misconception and the question of what constitutes trial related injuries. *Developing World Bioethics* 7(3): ii-iv.

Shapiro K, Benatar S (2005) HIV prevention research and global inequality: steps toward improved standards of care. *J Med Ethics* 31: 39-47.

Singh JA, Mills EJ. (2005) The Abandoned Trials of Pre-Exposure Prophylaxis for HIV: What Went Wrong? *PLoS Med* 2(9): e234.

Singh JA, Karim SSA, Karim QA, Mlisana K, Williamson C, Gray C, Govender M, Gray A (2006) Enrolling adolescents in research on HIV and other sensitive issues: lessons from South Africa. *PLoS Med* 3(7): e180.

Sugarman J, Dickert N (2005) Ethical Goals of Community Consultation in Research. AJPH 95, 1123-1127.

UNAIDS (2000; Third reprint, 2004). Ethical considerations in HIV preventive vaccine research. UNAIDS guidance document. Geneva: UNAIDS.

UNAIDS (2004) 2004 Report on the global HIV/AIDS epidemic. 4th global report. Geneva: UNAIDS/WHO.

UNAIDS (2007a) Ethical considerations in biomedical HIV prevention trials. UNAIDS/WHO guidance document. Geneva: UNAIDS. Available at: http://data.unaids.org/pub/Report/2007/jc1399-ethicalconsiderations_en.pdf.

UNAIDS (2007b) Good participatory practice. Guidelines for biomedical HIV prevention trials. Geneva: UNAIDS. Available at: http://data.unaids.org/pub/Manual/2007/jc1364_good_participatory_guidelines_en.pdf.

Upshur REG, Lavery JV, Tindana P (2007) Taking tissue seriously means taking communities seriously. *BMC Medical Ethics* 8(11).

Van de Wijgert JHHM, Shattock RJ (2007) Vaginal microbicides: moving ahead after an unexpected setback. *AIDS* 21 (18): 2369-2376.

Vaz L, Corneli A et. al. (2008) The process of HIV status disclosure to HIV-positive youth in Kinshasa, Democratic Republic of the Congo. *AIDS Care* 20 (7): 842-852.

Weijer C, LeBlanc GJ (2006) The Balm of Gilead: is the provision of treatment to those who seroconvert in HIV prevention trials a matter of moral obligation or moral negotiation? *Journal of Law, Medicine and Ethics* 34 (4): 793-808.

Woodsong C, Karim QA (2005) A Model Designed to Enhance Informed Consent: Experiences From the HIV Prevention Trials Network. *AJPH* 95, 412-419.

Wassenaar WR, Barsdorf NW (2007) The ethical involvement of women in HIV vaccine research in Africa: discussion paper developed for the African AIDS Vaccine Programme. *Women and Health* 45(1): 37-48.

Wikler D, Brock DW (2007) Population-level bioethics: mapping a new agenda. In: *Ethics, Prevention and Public Health.* Angus Dawson and Marcel Verweij (eds.). Oxford: Oxford University Press.

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