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**HIV Prevention Trials Network  
Ethics Guidance for Research**

*DRAFT*

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## **Preamble**

HIV disproportionately affects vulnerable populations, and because the social determinants of the AIDS pandemic encompass poverty, stigma, discrimination, and injustice, HIV prevention research requires the enrollment of people who are often vulnerable in multiple ways. The extent of vulnerability often parallels the magnitude of the risk for HIV and, correspondingly, HIV incidence rates. From a scientific perspective, the most desirable populations for HIV prevention research are therefore often the most vulnerable. There is thus a particular need to ensure that the conduct of research in these populations does not exploit this vulnerability.

In keeping with the highest scientific standards of the National Institutes of Health (NIH) sponsored HIV Prevention Trials Network (HPTN), the goal of this HPTN ethics guidance document is to foster best efforts and best practices in the conduct of HPTN research by raising awareness of ethical considerations, engaging network members at all levels in dialog about those considerations, and facilitating ethical decision-making at key points in the research process. This guidance emphasizes mutual accountability among peers and the thoughtful translation of ethical considerations into action. It does not, and cannot, carry the weight of regulatory authority.

The document is presented in 5 parts. The first part provides a brief overview of the HPTN and the ethics framework for the document; the second part provides a summary of each of the guidance points in a tabular format for easy reference; the third part outlines the mechanism of translating each guidance point into action; and the fourth part provides specifications and justifications for the guidance points. The fifth part provides background information on the ethical challenges that led to the development of this guidance and the ethical debates surrounding these challenges.

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**Acronyms**

ART	Antiretroviral Therapy
CAB	Community Advisory Board
CFR	Code of Federal Regulations
CL	Central Laboratory
CORE	Coordinating and Operations Center
CP	Concept Plan
CPA	Cooperative Project Assurance
CPRP	Cooperative Protocol Research Program
CRM	Clinical Research Manager (CORE)
DAIDS	Division of AIDS
DHHS	Department of Health and Human Services
DMC	HIVNET Domestic Master Contractor
EAC	External Advisory Committee
EC	Executive Committee
ETB	Efficacy Trials Branch
FHI	Family Health International
FHCRC	Fred Hutchinson Cancer Research Center
HIVNET	HIV Network for Prevention Trials
HPTN	HIV Prevention Trials Network
HPTU	HIV Prevention Trials Unit
HVTN	HIV Vaccine Trials Network
HVTU	HIV Vaccine Trials Unit

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IMC	HIVNET International Master Contractor
IDU	Injecting Drug Use
JHU	Johns Hopkins University
LC	HIVNET Laboratory Center
MO	NIH Medical Officer
MPA	Multiple Project Assurance
MRC	Manuscript Review Committee
NEC	Network Evaluation Committee
NIAID	National Institute of Allergy and Infectious Disease
NICHHD	National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
OAR	Office for AIDS Research
OHRP	Office for Human Research Protection (formerly OPRR)
PAB	Pharmaceutical Affairs Branch
PLG	Prevention Leadership Group
POC	Protocol Operations Coordinator (SDMC)
PRC	Protocol Review Committee
PSRC	Prevention Sciences Review Committee (DAIDS)
PT	Protocol Team
PTN	Prevention Trials Network
PY	Person Years

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QC	Quality Control
QA	Quality Assurance
RA	Regulatory Affairs
RCT	Randomized Controlled Trial
ROC	DAIDS Regulatory Operations Center
SAE	Serious Adverse Experience
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SDMC	Statistical and Data Management Center
SIV	Simian Immundeficiency Virus
SMC	Study Monitoring Committee
SOP	Standard Operating Procedures
SPA	Single Project Assurance
SSG	Scientific Steering Group (HIVNET)
STD	Sexually Transmitted Diseases
SWG	Science Working Group
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	US Agency for International Development
VPRP	Vaccine Prevention Research Program, DAIDS
VRDL	Viral and Rickettsial Disease Laboratory
WHO	World Health Organization

## **Introduction**

### **Purpose**

The HIV Prevention Trials Network (HPTN), funded by the National Institutes of Health (NIH), is one of the major U.S.-based sponsors of HIV prevention research in both the U.S. and international settings. To accomplish its mission of investigating and establishing new non-vaccine HIV prevention interventions, the HPTN must navigate a morally defensible path between ethical uncertainty and the public health imperative of halting a pandemic of unprecedented proportions. This document establishes a set of considerations for the ethical design and conduct of prevention research within the HPTN. It is designed to guide decision-making and practice for establishing research objectives within HPTN science working groups, selecting and developing protocols, and preparing for and implementing HIV prevention research. Because the HPTN is specifically concerned with HIV-prevention research, especially new methods of primary prevention with HIV infection as the primary research outcome, this guidance document predominantly concerns itself with this type of research.

The guidance should be taken into consideration as new concept proposals are being developed, and when approved research protocols are being implemented. Investigators should address the issues raised by each guidance point, and the HPTN review procedures should ascertain that each point has been 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 during implementation of the research. The resulting

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documentation should be reported to the HPTN PRC and PLG, and placed in the protocol files at CORE and on site.

This guidance document is built on HPTN aspirations. It is a compilation of best practices and accepted standards for the conduct of ethical research. With few exceptions, the actions outlined reflect procedures and strategies that are already being used within the HPTN, though perhaps not consistently. Implementing the guidance will therefore initially require some additional effort by HPTN members, and strategies for accomplishing this will need to be developed. Additionally, the document may need to be refined as experience using the guidance is garnered, new research is designed, or when significant events occur that affect the guidance for research already underway or on the “go” list. As such, this is a living document.

Ethical decision-making 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 the goal of this guidance is to 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.

### **An Ethics Framework for HPTN**

The guidance in this document describes ethical obligations related to research participants and communities from which research participants are drawn. Many obligations are procedural, that is, they describe the procedures by which HPTN will help to ensure that its research is designed and conducted in an ethically appropriate fashion and is aimed at promoting the welfare of HPTN research participants and communities. In some instances, the procedures to be followed cannot guarantee that the most desirable outcomes will be achievable. An inability to ensure desirable outcomes or to guarantee

desirable benefits does not preclude going forward with research, but it is obviously morally preferable if they can be achieved. The procedures outlined ensure that appropriate efforts will be made toward that end. Other obligations aim towards a goal of enhancing the conditions necessary for the health of all. They represent domains where creativity, partnership, and persistence are needed to more closely link HPTN research to HIV prevention practice specifically and public health practice more broadly.

Many obligations relating to research participants are well established in existing bioethics guidance documents and in the U.S. federal regulations for the protection of human subjects. Those established obligations are broadly referenced in this document but not discussed in detail. Obligations relating to research communities are less well established, and therefore receive somewhat greater attention here.

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**Summary of Guidance Points**

**Table 1. HPTN Ethics Guidance Points.**

<b>Guidance Points</b>
<i>Section 1. General Considerations</i>
Guidance 1.1-- HPTN research will be scientifically and ethically sound and include a meaningful process for community participation.
Guidance 1.2-- The HPTN will strive to advance ethical standards for research while respecting and adhering to local and U.S. regulatory standards concerning the ethical conduct of research.
Guidance 1.3-- The dignity of all participants in HPTN research is paramount.
Guidance 1.4-- The dignity of the communities from which HPTN participants are drawn must be upheld.
Guidance 1.5-- HPTN research will be designed and conducted so as to promote equality among research participants.
Guidance 1.6-- Every HPTN protocol will document the steps taken to insure that vulnerable populations are not unfairly burdened and that enrollment targeting vulnerable populations is appropriate with regard to the risks and the likelihood of potential benefit for those populations.
Guidance 1.7-- Every HPTN protocol will document the steps to be taken to minimize risks associated with the research and to mitigate research-related harms, including medical, psychological, social, and economic.
<i>Section 2. Meeting Local Needs and Priorities</i>
Guidance 2.1-- HPTN research should address a significant health risk that is a priority for the countries hosting the research.
Guidance 2.2-- The HPTN will provide support to help ensure that host country populations will benefit from the research it sponsors.

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<b>Guidance Points</b>
Guidance 2.3-- Infrastructure development for HPTN research should focus on local capacity building that is sustainable independent of the life of the research effort and provides a foundation for on-going benefit to the local community when the research is completed.
<i>Section 3. Care and Prevention</i>
Guidance 3.1—The HPTN will balance proposed intervention research against known effective HIV interventions, if any exist.
Guidance 3.2-- All HPTN research projects must ensure that effective means of prevention for HIV and STI transmission that would be practically achievable as a standard of care in the local setting are reasonably accessible by all people who are screened or enrolled.
Guidance 3.3— In designing and conducting its research, the HPTN will explicitly consider the local standards of care, the implications of those standards for research participants, and the potential impact of research-associated care on the local community.
Guidance 3.4-- In order to conduct HIV prevention research in settings where standards of care are poor, the HPTN will consider options for contributing to the improvement of the local infrastructure so that the standard of care might be improved.
<i>Section 4. Informed Consent</i>
Guidance 4.1—Each HPTN site involved in a research project will develop, document, and implement a meaningful informed consent process unless the research meets accepted criteria for waiving informed consent.
Guidance 4.2-- The informed consent process for each HPTN research project will accurately describe the procedures to be followed and the components of care that are to be made available as a result of research participation, including whether access to any or all of those components will be sustained once research participation ends or the research is completed.
Guidance 4.3. The protocol team and each HPTN site involved in a research project will consider the need for continuing consent by participants and establish appropriate mechanisms for addressing such needs.

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## Guidance Considerations

### Section 1. General Principles

***Guidance 1.1: HPTN research will be scientifically and ethically sound and include a meaningful process for community participation.***

*Scientifically sound research:* The HPTN Science Working Groups (SWGs), the Protocol Review Committee (PRC), and the DAIDS Prevention Science Research Committee (PSRC) have primary responsibility for oversight on the scientific soundness of proposed HPTN concepts and proposals. The established review process ensures that the research proposed by the Network meets the highest scientific standards. Quality assurance measures are also in place during the implementation of the protocols through SCHARP and internal and external study monitoring to insure that the research will generate valid, reliable data. In addition to these measures, HPTN investigators should conduct formative research during the site preparation and protocol development phase to validate measures and data collection strategies, or to develop alternative measures and strategies if local conditions are likely to influence the validity, reliability, or generalizability of the resulting data in ways that have not been previously explored and addressed.

*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 given equal weight to scientific considerations. The HPTN will institute the following steps to ensure that ethical considerations are appropriately addressed and to facilitate the DAIDS regulatory review and the local IRB review requirements established under U.S. and collaborating country regulations:

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1. **Concept Proposals:** Each new concept plan submitted to the EC for review will include a brief statement indicating whether there are any special ethical considerations associated with the proposed research. The PRC/PSRC concept proposal review process will include simultaneous review by the EWG chair or the chair's designee, as part of the already established joint review by the PRC chair/designee, SDMC statistician/designee, and two representatives from the PSRC; the PRC chair will have responsibility for coordination as established in existing policy. Investigators are encouraged but not required to consult with the EWG in the earliest stages of development of a concept proposal to insure that ethical challenges are recognized and surmountable. This requirement applies only to concept proposals developed after the adoption of this guidance document by the EC; it does not require retroactive action.
  2. **Protocol Development:** If the PRC or SWG review process indicates that significant ethical challenges exist, the protocol team will consult with the EWG to identify someone with an appropriate level of expertise in both the science and ethics of the proposed research to serve as a consultant to or, if appropriate, as a member of the protocol team. 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. The reason for including ethics consultation during protocol development when significant ethical challenges exist is to reduce the likelihood that research timelines will be delayed due to a failure to fully address the ethical challenges prior to PRC, PSRC, and IRB/EC reviews of protocols. Early consultation should also enhance HPTN efforts at developing consensus across the Network where this is feasible and to ensure that ethical decision-making is appropriate. It may also serve to highlight areas where this guidance needs to be reconsidered.

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- For protocols already in development at the time this guidance is issued, HPTN Protocol Team Chairs should ensure that the protocol files include documentation concerning any ethical issues identified to date and the strategies being considered or already in place to address these issues.
3. **Protocol Review:** As part of the PRC protocol review process, an ethics review team will be established in consultation with the EWG; this team will parallel the existing PRC science and statistics teams and provide a pool of potential reviewers (review by the full team is not required or expected). As with the science and statistics reviews, the ethics review of new protocols will occur simultaneously with and as an integrated part of the PRC protocol review process, with the PRC chair having responsibility for coordination as established in existing policy. A primary ethics reviewer and, if appropriate, one or more secondary reviewers from the ethics review team will be designated for each protocol under review. The primary reviewer will have responsibility for synthesizing and reporting any comments from secondary reviewers, as part of the PRC review on the review call and in written notes to the PRC chair, as described in the PRC protocol review process. 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 PRC ethics review team will be comprised of people with an appropriate level of expertise in both the science and ethics of HIV prevention research.
  4. **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. The DAIDS Monitoring Contractor will assess site adherence to federal human subjects protections and other regulations. Study assessment activities conducted by CORE staff will include attention to ethical concerns, and checklists to facilitate documentation of ethics-related activities will be developed in

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consultation with the EWG. Assessment of ethics-related activities will complement monitoring for compliance with regulatory requirements for human subjects protections, with the goal of supporting sites in their efforts to meet those requirements and to achieve the greatest benefit for participants and communities.

5. Dissemination of Results and Findings: To insure that HPTN manuscripts appropriately address any pertinent ethical issues the Manuscript Review Committee (MRC) will include members with an appropriate level of expertise in both the science and ethics of HIV prevention research. The process for ethics review will be fully integrated with the existing MRC review procedures. Investigators are also obligated to develop plans for sharing results with their respective communities and local relevant stakeholders; this should be negotiated with the local Community Advisory Boards as part of site and research implementation preparatory activities.

*Community participation:*<sup>1</sup> For the purposes of HPTN research, a community is the group of people who will participate in or are likely to be affected by or have an influence on the conduct of the research. The community may include:

- The group from which research participants will come (e.g., a specific group such as 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; and
- Influential or key individuals from this community, such as traditional or governmental leaders, professionals or volunteers who work with HIV prevention or research programs in the community in which the research will be conducted, and members of the healthcare and medical community.

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<sup>1</sup> This section is derived from materials developed by the HPTN Community Working Group.

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Oversight of the community preparedness and consultation process rests with the HPTN Community Working Group. A community advisory mechanism has been established at each of the HPTN sites, with the most common approach being the creation of a Community Advisory Board (CAB). Each site's advisory structure may vary based on local needs and direction. CABs provide advice on scientific and ethical issues regarding study design, recruitment and protection of study volunteers. Each CAB will develop their own mission statement and operating guidelines. It may also be appropriate to seek input beyond the CAB at some stages in the research process. For example, during concept proposal development it may be appropriate to meet with opinion leaders and stakeholders from a wide range of communities who potentially stand to benefit from the research to ensure generalizability and utility of the results nationally or regionally.

Sustained relationships and communication with community members are the responsibility of the Principal Investigator at each site, who should include sufficient funds in the annual budget request to support participation of community representatives in protocol development, including attendance at face-to-face protocol team meetings, local transportation costs, participation in conference calls, and participation in training. Involvement and participation of community members will be supported 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 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 a way that is accessible and appropriate for community representatives.

Community representatives 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, and should strive to ensure that all significant perspectives are raised including views of community members or groups that may differ from their own. CAB members are expected to attend local CAB meetings, provide feedback on issues under discussion, voice concerns from the communities and study

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participants, and disseminate 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 other 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 and with the Principal Investigator, and to actively participate in HPTN Community Working Group (CWG), regional community working group (RWG), and protocol-specific community conference calls.

The HPTN CORE is responsible for outlining steps to develop, maintain, support, and encourage the full participation of community representatives in all phases of the research process. This includes plans for community education, training, recruitment, ongoing orientation, and facilitate access to participation on science direction working groups and network governance committees.

***Guidance 1.2: The HPTN will strive to advance ethical standards for research while respecting and adhering to local and U.S. regulatory standards concerning the ethical conduct of research.***

The processes of ethics consultation and review outlined in Guidance Point 1 will support and comply with, but not be limited to, U.S. federal regulations for the protection of human subjects. Compliance with U.S. regulations must at all times be balanced with local requirements and standards as well as compelling and relevant international guidance documents. If conflicts arise between local or international and U.S.-based requirements, HPTN will provide the resources and support needed to resolve the conflicts, preferably through fostering meaningful, informed discussion among all parties. The HPTN will strive to advance ethical standards for research by asking what is achievable in addition to what is required.

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***Guidance 1.3: The dignity of all participants in HPTN research is paramount.***

HPTN research represents a means to the goal of effective HIV prevention and not an end in itself. The dignity of HPTN research participants must not be intentionally sacrificed to achieve research objectives. The fundamental step necessary to preserve dignity is to approach participants as partners in the research endeavor, establishing non-judgmental relationships based on openness and trust.

Where participants experience stigma, discrimination, prejudice, or other affronts to dignity in their daily lives, the HPTN research setting should ideally provide a haven that promotes personal dignity. Research staff should actively support autonomous decision-making, including respect for every participant's right to limit or terminate research participation despite the need for high retention rates in trials. Incentives for participation should be established in consultation with CABs and local ethics committees to ensure they are appropriate to the local context and contribute to participants' sense of dignity; autonomy must not be undermined through use of undue inducements or coercive practices. Participants' desires for privacy must be respected and confidentiality maintained to the greatest extent possible consistent with local laws; participants should also be fully informed of any limits placed on confidentiality by local laws, for example, reporting requirements.

Where research participants are vulnerable or otherwise lacking in power it is incumbent on health workers, researchers and others in relatively powerful and influential positions to avoid the perception of coercion.

***Guidance 1.4: The dignity of the communities from which HPTN participants are drawn must be upheld.***

It is recognized that communities will vary with regard to the amount of coherence (i.e., unity in action, experience, knowledge, values, and beliefs) they exhibit as well as the extent to which individuals identify with a particular community. Depending on the level

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of coherence, community protections are likely to be enhanced through mechanisms for community consent and consultation(1), and through the establishment of partnerships. The HPTN recognizes that the partnerships between a community and a research project can develop in many different ways over time. As a result, the ways a research project receives guidance from the community and shares information about research activities may also vary. HPTN research projects minimally require community consultation, which can be defined as “the involvement of community representatives to a limited degree in research planning, informing the community as a whole of the research at its start and as progress is made, consulting with community representatives regarding the disposition of data, and providing them with a draft report on which to comment”(1) (page 1143). HPTN investigators are strongly encouraged to exceed this minimal requirement and establish more fully participatory projects based on partnership and shared decision-making.

In situations where community coherence is high and a legitimate political authority exists, for example, a tribal council with authority to make binding decisions on behalf of its members, then HPTN researchers should seek formal support from this authority as part of research preparations. The legitimacy of the authority for the research target population, the mechanisms for obtaining community consent, and additional mechanisms for insuring the autonomous decision-making of individual participants should be tailored to the particular features of the community and will likely need to be examined through formative social science research. These formative findings as well as the procedures and processes used in each setting should be carefully documented.

If community coherence is minimal to nonexistent, HPTN sites must consider creative mechanisms to support consultation and build partnership with the target population. A variety of activities and strategies can be used to achieve this objective, including but not limited to focus group discussions, outreach, informal and formal meetings with community leaders, feedback meetings between stakeholders and research team members, and educational theatre. Requests to forego all efforts at community

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consultation and partnership as part of HPTN research at a local site must be justified on the basis of the potential for harm to research participants or a similarly compelling reason and submitted for approval by a special review committee comprised of the PRC chair, EWG chair, and CWG chair (or their designates), with approval requiring at least two votes in support of waiving the requirement.

***Guidance 1.5: HPTN research will be designed and conducted so as to promote equality among research participants.***

Each HPTN research site should treat like participants in like ways. Care should be taken to avoid discriminatory or stigmatizing distinctions between research participants in different research studies, and differences in treatment should reflect substantive differences in need. For example, enrollment of particular individuals in research should not be affected by gender unless the protocol addresses a gender-limited HIV prevention issue. Similarly, a person who is screened for syphilis in research A at a particular site should be able to receive the same quality of care for syphilis as a person screened in research B at the same site. One obvious exception to this approach would be where participants are assigned to treatment and control arms as part of the research design.

To ensure that HPTN efforts promote equality and that the benefits and burdens of research are distributed fairly, the project portfolio and enrollment data from HPTN research should be evaluated by the EC on a regular basis and adjustments sought should significant disparities be identified.

***Guidance 1.6: Every HPTN protocol will document the steps taken to insure that vulnerable populations are not unfairly burdened and that enrollment targeting vulnerable populations is appropriate with regard to the risks and the likelihood of potential benefit for those populations.***

To avoid exploitation of vulnerable populations, site selection criteria must satisfy not only epidemiological criteria but social criteria as well, including:

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- Evidence that participants can be recruited without creating or increasing risks of stigmatization, discrimination, prejudice, or violence. Throughout the world, such risks are frequently associated with HIV, AIDS, and many of the behaviors that facilitate HIV transmission. HPTN research should not add to this existing burden of social harms; rather, it should strive to minimize them. For example, if the research were to target HIV-infected mothers, the researchers should be able to demonstrate that such mothers can be recruited without compromising their confidentiality and increasing the likelihood that they will be stigmatized. This could require the ability to ensure that participants can be recruited without being labeled in a stigmatizing way, or through supporting community-based efforts to reduce HIV-related stigma.
  - Evidence that risks directly associated with the research will not exacerbate existing or create new vulnerabilities in the target population. For example, it may be important for researchers to verify that microbicide use will not expose women in a trial to accusations of infidelity and potential domestic violence. This could include the use of community-based strategies to reduce misunderstanding, such as outreach and education, or clinic-based strategies to empower participants, such as family counseling and social support.
  - Evidence that the research is likely to generate benefits appropriate to the needs of the target population regardless of whether the experimental intervention proves successful. For example, community outreach, education, and mobilization on HIV and STI prevention included as part of the trial infrastructure could provide broad benefits.

For populations without experience participating in HIV prevention research or similar research, it may be necessary to conduct formative social science research to adequately address these issues.

For research already underway, or where project sites have been selected and implementation is imminent, participating sites should document the extent to which the criteria outlined above are satisfied and whether any changes are indicated.

*Guidance 1.7: Every HPTN protocol will document the steps to be taken to minimize risks associated with the research and to mitigate research-related harms, including medical, psychological, social, and economic.*

Strategies for minimizing medical risks to participants include provision of appropriate clinical monitoring and assurance of treatment for research-related injuries and adverse events; this may require advocacy with research sponsors and others to establish funds for this purpose. Psychological risks can be minimized through provision of appropriate counseling for distress and emotional upset related to HIV testing and sensitive research questions. Many social risks can be attenuated by developing appropriate measures to protect confidentiality and through services provided by a social worker for referrals and support. Economic risks can be minimized by including provision of appropriate compensation for time missed from income-generating activities and other costs incurred during research such as transportation and childcare.

Risks should also be addressed with regard to communities. Medical risks to partners should be evaluated, including, for example, side effects of microbicides for male partners of female trial participants. Psychological risks to family members should be considered, for example, stress or depression resulting from research-related disparities in family members' ability to access care. Social risks, particularly stigmatization of groups of people as a result of targeting by researchers, need to be carefully evaluated. Community-level economic risks to consider include the siphoning off of limited resources, including health professionals and clinic space, for the conduct of research. CABs should be involved in both exploring and mitigating community-level risks associated with HPTN research.

If knowledge about potential risks is lacking, especially with regard to social or economic risks for persons, or community risks in general, it may be necessary to conduct formative social science research as part of site preparatory activities. Such research may

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include collection of data on existing social and sexual norms; issues around stigma and discrimination; the implications of HIV/AIDS disclosure; gender norms; and household and community-level decision-making processes. This information may be useful in informing the design and conduct of trials, informed consent procedures, and community education plans, and may also facilitate the translation of successful trial outcomes into successful community-level programs.

Minimization of risks also raises the issue of who will pay for treatment of research-related injuries. HPTN and its research sponsors, including DAIDS, are obligated to take steps to address this issue explicitly and it is desirable to create mechanisms to insure that anyone who suffers harm as a direct result of participation in HPTN research will receive appropriate care and services to mitigate that harm.

## **Section 2. Meeting local needs and priorities**

***Guidance 2.1: HPTN research should address a significant health risk that is a priority for the countries hosting the research.***

There is no question that HIV prevention is a public health priority for all countries where HPTN research is currently being conducted. Nonetheless, each HPTN research protocol represents a carefully crafted effort to identify effective interventions for targeted components of a global epidemic. Verification of the extent to which this targeted component is a local health priority should be sought. Examples of appropriate forms of verification include but are not limited to government statements or reports indicating health priorities, epidemiologic evidence of the local need for the interventions, and confirmation that the research addresses a local health priority in letters of support from or reports of meetings with Ministries of Health officials, local public health officials, and non-governmental organizations providing significant health care or services in the local community.

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For research already approved locally or already in the field, verification in the form of official letters of support or similar types of documentation should not be sought if it will precipitate distrust about the original intent of the research. Instead, efforts should focus on facilitation of the translation of positive research results into effective local programs.

***Guidance 2.2: The HPTN will provide support to help ensure that host country populations will benefit from the research it sponsors.***

Responsibility for ensuring that adequate resources and support exist for enhancing benefit rests at all levels of the HPTN. Implementation of successful trial interventions and sustainability of infrastructures for care are priority areas.

- Protocol teams should identify challenges that may exist for insuring benefit to host country populations from the proposed research.
- Investigators should identify and link with host country partners who will be critical for the successful translation of positive research results into local programs.
- Investigators should explore partnerships to link research knowledge, expertise, and infrastructure to local capacity building.
- The EC and financial sponsors should support linkages and meetings with Ministries of Health, USAID, CDC, international aid and development organizations, foundations, NGOs, pharmaceutical companies, and other partners who could facilitate the transfer of research benefits to host countries.

***Guidance 2.3: Infrastructure development for HPTN research should focus on local capacity building that is sustainable independent of the life of the research effort and provides a foundation for on-going benefit to the local community when the research is completed.***

When the conduct of HPTN trials requires substantial investment in the development of clinical and laboratory capacity, whenever possible this capacity should be available to non-research staff and patients at cost. Infrastructure and technology should be

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developed in ways that can be transferred to local providers, including training as appropriate. Support for such transfers should be actively sought through partnering with developmental aid sponsors. Examples of technology that could be transferred for local use include lab equipment and training of technicians for CD4 and viral load testing for host country ARV program use, expanded lab support for STI syndrome management (e.g., syphilis serology, vaginal microscopy, gonorrhea culture, antibiotic sensitivity testing), and use of colposcopes in developing public sector cervical cancer screening programs.

### **Section 3. Care and Prevention**

***Guidance 3.1: The HPTN will balance proposed intervention research against known effective HIV interventions, if any exist.***

This guidance point addresses what care is to be provided to participants in the control arm of a trial; considerations regarding preventive care and services related to study and screening outcomes are discussed under Guidance 3.2, and considerations regarding non-study related care procedures are discussed under Guidance 3.3.

HPTN research design requires selection of comparison or control arms that reflect best practices in HIV prevention while generating scientifically valid results and useful data for developing prevention programs. A prescriptive approach to designing comparison or control arms within HPTN cannot satisfy all of these criteria. Therefore, proposed research designs must include consideration of each of the following questions:

- Are there other known effective interventions that could be 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 available to research participants in the proposed research sites?

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- 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?

The protocol team should address each of these questions and document the conclusions reached. For research that is still in the developmental phase, this information should be presented as part of the review process and filed with review materials. For each HPTN research protocol currently implemented, they should be addressed in a separate memo that is submitted as a report to the PLG and filed with the project files at CORE and on site.

If the research design is predicated on the lack of local resources to implement known effective HIV interventions, HPTN must carefully consider whether the research serves to bolster an inadequate and modifiable status quo. If such is possible, HPTN should consider whether a period of strong advocacy for improved prevention programs is desirable before or in tandem with investing resources in the testing of alternative intervention designs.

***Guidance 3.2: All HPTN research projects must ensure that effective means of prevention for HIV and STI transmission that would be practically achievable as a standard of care in the local setting are reasonably accessible by all people who are screened or enrolled.***

This guidance point addresses preventive care and services related to study and screening outcomes; considerations regarding what care is to be provided to participants in the control arm of a trial are discussed under Guidance 3.1, and considerations regarding non-study related care procedures are discussed under Guidance 3.3.

“Effective means of prevention” refers to those interventions for which evidence of effectiveness exists and for which there is no reasonable basis for questioning the effectiveness of the method in the local research setting. If provision of the intervention creates the potential for undue inducement to participate in the research or for locally unacceptable dual standards of care, then resolution should be sought as outlined in Guidance Point 3.4 below.

“Reasonably accessible” means the services are free or at a cost within the means of research participants, and can be implemented safely within the participants’ community. In general, services may be provided through referral if the referring clinic meets these criteria for accessibility or if direct provision of the services would critically undermine the capacity of the research staff.

“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 that 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.

As a minimal base, every HPTN research protocol will explicitly consider the need for HIV voluntary counseling and testing, HIV and STI risk reduction counseling, and condoms provided to research participants. Beyond this minimal base, each site and protocol team may identify additional services to be provided, with considerable room to expand beyond this minimum. To assist sites and protocol teams in determining appropriate prevention services, each of the Science Working Groups (Microbicide, Behavioral, STI, ARV, Perinatal, Substance Use) will compile a list of candidate interventions relevant to the prevention modality of the group to serve as guidance to all

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HPTN protocol teams on this issue. The list will include any necessary caveats concerning how variability in local settings would be likely to impact the effectiveness of the methods. Should an HPTN protocol team or HPTN site implementing a protocol believe that a known method of prevention would be inadequate and, therefore, need not be provided in a local research setting, this must be communicated to the chair of the appropriate Science Working Group (or the chair's designee) and the EC along with supporting evidence and concurrence obtained.

***Guidance 3.3: In designing and conducting its research, the HPTN will explicitly consider the local standards of care, the implications of those standards for research participants, and the potential impact of research-associated care on the local community.***

This guidance point addresses non-study related care procedures; considerations regarding what care is to be provided to participants in the control arm of a trial are discussed under Guidance 3.1, and considerations regarding preventive care and services related to study and screening outcomes are discussed under Guidance 3.2.

As part of research preparations at protocol sites and as indicated under Guidance 4.2, the requirements for preventive, clinical, and laboratory care associated with the research should be explicitly outlined and each participating site should identify the extent to which that care exceeds what is currently available to the local target population. This will identify the extent to which participant care exceeds local standards, and indicate where inducements for participation and sustainability of care at research termination may be a concern.

As indicated under Guidance 4.2, a systematic assessment of the care and services needed to implement HPTN research, and the extent to which they are accessible outside the research context in the communities where the research takes place, will be made prior to implementing new research projects. As part of this process, participating sites should

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indicate if other care and services are desirable as benefits, given the local health care context. Resources to conduct the assessment are to be included as part of the protocol or site preparation budgeting process.

The results of the assessment are to be presented to key stakeholders for discussion leading to consensus regarding appropriate standards of care in the local research contexts.(2) Potential stakeholders include

- Research participants or their advocates
- Local health care providers or their advocates
- Local agencies or offices of relevant government entities (e.g., ministry of health, national AIDS control program, population office)
- HPTN investigators for the site
- HPTN protocol co-chairs for the research
- HPTN investigators conducting other research projects at the site
- CAB members for the site
- Educators
- Media representatives

The exact nature of the consensus-building process is not prescribed here, as each research protocol may present unique challenges. However, the process should include facilitation by someone who is not directly involved with the research, opportunities for open dialog by all stakeholders, clarity about the ethical question to be addressed, and commitment to reaching a timely decision. Strategies for enhancing the efficiency of this decision-making process should be discussed by the HPTN Science Working Groups, CWG, and EWG, including the option of establishing generally agreed upon (prima facie) standards for the provision of care during all HPTN research. Such standards should be periodically reviewed with reference to new data, consensus statements, and recommendations regarding care, and revised if substantively warranted and appropriate.

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***Guidance 3.4: In order to conduct HIV prevention research in settings where standards of care are poor, the HPTN will consider options for contributing to the improvement of the local infrastructure so that the standard of care might be improved.***

If care is provided during a research project that is not otherwise generally available in a community, and research participants would be in some way harmed as a result of withdrawing this care, it is desirable for the HPTN to seek resources and build capacity for that care so that access can be maintained once the research ends. This will likely require efforts to partner with organizations and sponsors whose primary mission is to provide support for programs and services, such as local governments, the Elizabeth Glaser Pediatric AIDS Foundation, the Bill and Melinda Gates Foundation, Médecins Sans Frontières (MSF), UNAIDS, USAID, and CDC. Efforts to sustain access should be documented and outcomes of those efforts reported as part of site assessments. Options for contributing to the improvement of local conditions should be measurable and sustainable, and may include:

- Capacity building for existing health care facilities, for example, through training and public health infrastructure development.
- Provision of basic services and care to community members, regardless of research participation.
- Advocacy for and fostering of relationships to bring in new resources for health care in the community.

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## Section 4. Informed Consent

***Guidance 4.1: Each HPTN site involved in a research project will develop, document, and implement a meaningful informed consent process unless the research meets accepted criteria for waiving informed consent.***

The informed consent process for HPTN research requires explicit consideration at both pre-enrollment and enrollment.<sup>1</sup> The *pre-enrollment stage* includes rapport-building, information-sharing, and consultation activities in the local community; lexicon development for translation of technical terms; translation of informed consent materials; and development of the informed consent document and training of staff in the administration of informed consent. The *enrollment stage* encompasses the specific way in which informed consent is administered, and documentation of informed consent. Where appropriate, the protocol team will develop mechanisms to evaluate comprehension of the informed consent process. A variety of strategies are suitable for this purpose, including use of informed consent comprehension checklists administered by clinic counseling staff after participants are given information about the research and have had an opportunity to have their questions about it answered, and open-ended questions about key informed consent elements asked of participants during review of the consent information. Additional data collection approaches may be developed, such as exit interviews to be conducted with a sub-sample of participants at selected follow-up visits and periodic checklists of informed consent comprehension that are part of routine assessment procedures. The strategy used should be appropriate for the research population and context.

In addition to monitoring comprehension of informed consent throughout the project, investigators may wish to collect information on participant, provider, and community perceptions of the informed consent process. This information could be collected during site visits providing technical assistance, and/or quality assurance tasks, as well as review of relevant documents created throughout the course of research implementation. Such

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activities could compliment and draw upon existing monitoring and evaluation efforts, CWG activities, and routine HPTN CORE study assessment.

***Guidance 4.2: The informed consent process for each HPTN research project will accurately describe the procedures to be followed and the components of care that are to be made available as a result of research participation, including whether access to any or all of those components will be sustained once research participation ends or the research is completed.***

In order to minimize the likelihood of a therapeutic misconception, the research staff must themselves fully understand which procedures are experimental, which are provided as a non-experimental but necessary part of the research design, and which are provided solely as a benefit to the participant. To achieve this level of understanding, HPTN site preparations for the implementation of specific research protocols need to include the construction of a table summarizing

- each element of care to be provided to research participants;
- whether that element of care is part of the experimental aspects of the research project;
- whether that element of care is linked to non-experimental research design elements such as screening or secondary outcome measures; and
- whether and how long access to that element of care will be sustained at the end of research participation.

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. For previously approved protocols, if the currently approved informed consent form template does not accommodate the information outlined above, the information should nonetheless be provided to participants as supplemental information during the informed consent process for new participants and at the next follow-up visit for participants already enrolled in the research.

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<sup>1</sup> This section is derived in part from materials developed and written for the HPTN by Cynthia Woodsong,

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***Guidance 4.3. The protocol team and each HPTN site involved in a research project will consider the need for continuing consent by participants and establish appropriate mechanisms for addressing such needs.***

Depending on the particular research project and experiences during the conduct of the research, there may be an obligation during the *research continuation stage* to include on-going assessments of comprehension, information sharing, correction of misunderstandings on the part of participants, and rumor management within the community regarding the research. Of particular concern is consideration of the need for verifying that research participants continue to participate in an informed and autonomous manner. Conditions warranting assessments of continuing consent and mechanisms for assuring that consent include(3):

- Material, significant changes in the research’s purpose, risks, potential benefits, requirements, or alternatives warrant *reconsent* on a par with the procedures in place for initial consent including, if appropriate, assessments of comprehension. Wendler and Rackoff define a material change as one “that is relevant to whether research participation is consistent with subjects’ preferences and interests” and a significant change as one “that has a reasonable likelihood of affecting whether research participation is consistent with subjects’ preferences and interests” (page 3).
- Changes that are material but not significant warrant *on-going consent* through verbal disclosure on the part of the research staff and verbal agreement on the part of the participant, with documentation of the disclosure and agreement to the participant’s study file.
- For longitudinal research, *reaffirmation of willingness to participate* is warranted through verbal agreement at each follow-up contact of two months or longer; documentation to the study file is not necessarily required.

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- If verbal or non-verbal indications of *dissent* or discomfort with participation are noted, study staff should seek to identify and address the problem, and remind participants that their involvement in the research is voluntary and they are free to withdraw.

## Specifications and Justifications for Guidance Points

### Section 1: General Principles

***Guidance 1.1: HPTN research will be scientifically and ethically sound and include a meaningful process for community participation.***

A fundamental ethical requirement for research is that it be scientifically sound, based on the rationale that it is never appropriate to expose participants to the risks and burdens of research unless the research will in some way advance scientific understanding. Sound research design is essential to ensuring that something will be learned as a result of the research efforts that contributes to improved health.(4) At the same time, the desire to advance knowledge should not supercede the interests of persons or communities.(5)

Justice mandates that research not only meet the needs of scientists to advance understanding, but that the research also comports with local needs and priorities.(4;5) Communities inevitably face a series of choices that reflect their unique needs and priorities. Whether to participate in particular research efforts is but one of these choices and as a matter of respect, investigators should understand that discussions surrounding a proposed research effort necessarily involve balancing multiple choices for communities.(1;6)

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***Guidance 1.2: The HPTN will strive to advance ethical standards for research while respecting and adhering to local and U.S. regulatory standards concerning the ethical conduct of research.***

The US regulatory standards for research provide an important framework for incorporating the consideration of accepted ethical principles (that is, respect for persons, beneficence, and justice). This framework includes assessment and oversight by local review boards to insure that these principles are met in the assessment of research as well as the need to obtain informed consent for participation in research. Nevertheless, as in adopting any regulatory approach, there can be confusion regarding its application and a privileging of form over substance. To merely meet the letter of this regulatory framework is insufficient for much health related research, especially that which poses significant risks, benefits, and opportunities for those involved. With this in mind, it is incumbent upon those involved with research to have a thorough knowledge and understanding of the rationale for regulatory provisions so that, in addition to meeting the requirements of the regulatory framework, the spirit of the ethical principles is adopted in research endeavors. Of note, such an understanding can be appropriately used to minimize the regulatory burden. For example, the regulatory framework provides mechanisms for modifying the informed consent process so that it is consistent with local needs and expectations while also maintaining profound respect for the individuals who are being asked to participate in research. But effective use of those mechanisms requires an understanding of the underlying ethical principles.

Local regulations and standards for the ethical conduct of research carry the same weight and authority as U.S. regulations and standards. HPTN researchers should have a clear understanding of the local standards and requirements. International collaborations by their very nature require sensitivity to areas where differing standards may apply, and be prepared to lead the way in negotiating such differences in ways that maximize benefits for all parties.

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***Guidance 1.3: The dignity of all participants in HPTN research is paramount.***

A centerpiece of national and international declarations concerning the ethical aspects of research is attention to the dignity of participants in research. A common mechanism for respecting dignity involves obtaining meaningful informed consent from participants. However, dignity can also be compromised in several other ways. These include the stigma of particular diseases; if the concerns, fears, aspirations, and needs of participants are handled inappropriately during the design and conduct of research; and if participation threatens participants' ability to otherwise engage in community life.

Affronts to dignity run counter to efforts to improve health and well-being. Article 1 of the Universal Declaration of Human Rights states that “All human beings are born free and equal in dignity and rights.” While HPTN may not have the authority, influence, or resources to assure the rights of all research participants, it is fully within its power to assure their dignity in the context of its research endeavors.

***Guidance 1.4: The dignity of the communities from which HPTN participants are drawn must be upheld.***

It is now recognized that communities as well as persons can be harmed as a result of biomedical research especially with regard to stigmatizing diseases. For example, some Ashkenazi Jews have raised concerns that research on genetic determinants of cancers among their members may lead to discrimination(6). Epidemiologic investigations in the early days of the AIDS epidemic led to stigmatization of and discrimination against Haitians, gay men, and others identified as “risk groups” for the disease(7) (pages 101-103). Though the intent of HPTN research is to benefit all people affected by HIV, care must be taken to avoid winning this benefit at the cost of communities.

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***Guidance 1.5: HPTN research will be designed and conducted so as to promote equality among research participants.***

The formal principle of justice requires that equals be treated as equals. While determining what constitutes equality can at times be difficult, there is global consensus that persons ought to be considered as equals regardless of race, ethnicity, religion and gender. Accordingly, HPTN research needs to be developed in synchrony with this assessment of equality at each stage of development. Interventions should be targeted for development in such a way that they are sensitive to these considerations and that the individuals selected for participation are not exploited through considerations of race, ethnicity, religion, or gender. As such, all those screened and selected for HPTN research must be treated as equals. Further, it is desirable for the HPTN to promote equality through modeling equal respect and, where appropriate, to developing measures designed to promote the achievement of equality within complex social systems.

***Guidance 1.6: Every HPTN protocol will document the steps taken to insure that vulnerable populations are not unfairly burdened and that enrollment targeting vulnerable populations is appropriate with regard to the risks and the likelihood of potential benefit for those populations.***

A prominent conception of the principle of justice is to protect the least well off and to maximize their well being to the extent possible. Therefore, it is important for the HPTN to avoid wherever possible harming those who would be most vulnerable, even though it might be more convenient or expeditious to conduct the research with such populations. The HPTN as a whole is accountable in this decision-making process and thus these decisions need to be made explicit through discussion and documentation.

***Guidance 1.7: Every HPTN protocol will document the steps to be taken to minimize risks associated with the research and to mitigate research-related harms, including medical, psychological, social, and economic.***

Based on the principle of beneficence, benefits to participants should be maximized and risks minimized. In assessing risks it is essential to do so in a comprehensive manner so that each of these components of risk is considered. In assessing these aspects of risk, consideration should also be given to their likelihood and magnitude.

## **Section 2. Meeting local needs and priorities**

***Guidance 2.1: HPTN research should address a significant health risk that is a priority for the countries hosting the research.***

Based on the principle of justice, the concerns of local communities need to be considered in light of the objectives of the overall research agenda. Because communities bear considerable risks from participation and bear many of its burdens, it is essential to meet their needs. Explicit consideration of these concerns and documentation of the process, promise to help meet this requirement.

***Guidance 2.2: The HPTN will provide support to help ensure that host country populations will benefit from the research it sponsors.***

In return for bearing the burdens and risks of research participation, local communities that participate in the research should stand to benefit from any positive findings of the research. Relationships that are established to support a research effort should include frank discussions and agreements about the possibility of long-term commitments by both sponsors and host countries considering the range of possible outcomes from the research.

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***Guidance 2.3: Infrastructure development for HPTN research should focus on local capacity building that is sustainable independent of the life of the research effort and provides a foundation for on-going benefit to the local community when the research is completed.***

Establishing an infrastructure within which to conduct research requires a significant investment of resources. Prudence suggests that it would be sensible to establish this infrastructure in such a way that it is maintainable following completion of the research. At the same time, creating a sustainable infrastructure provides an additional benefit to participation and helps meet the needs of many communities.

### **Section 3. Care and Prevention**

***Guidance 3.1: The HPTN will balance proposed intervention research against known effective HIV interventions, if any exist.***

While local conditions may create situations that provide unique opportunities to research particular interventions, it is inappropriate to exploit these conditions solely for the sake of advancing a particular research agenda. Rather, where safe, effective, affordable, and appropriate interventions might be introduced and serve to ameliorate substantial human disease and suffering, efforts should be taken to improve the local setting to effectuate these changes, prior to considering whether to embark upon a research intervention.

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<sup>2</sup> The Willowbrook hepatitis experiments provide an important example of the ethical issue at stake. In these experiments retarded, institutionalized children were injected or inoculated with hepatitis so as to study the natural history of the disease and to develop treatments. The researchers argued that the experiments were ethical on the grounds that hepatitis was so prevalent at the institution that the children would have become infected anyway. Beauchamp and Childress(11) (p. 429) note that alternative ways to control hepatitis existed and quote Goldby, that the physician's "duty is to improve the situation, not to take advantage of it for experimental purposes."

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The central goal of the HPTN is the prevention of the transmission of HIV-infection. This goal must always be considered prior to any research initiative.

***Guidance 3.2: All HPTN research projects must ensure that effective means of prevention for HIV and STI transmission that would be practically achievable as a standard of care in the local setting are reasonably accessible by all people who are screened or enrolled.***

The ultimate goal of HPTN research is the prevention of HIV infection and AIDS. Although existing methods of prevention are not without their own problems such as inadequate efficacy and cultural acceptability, HPTN researchers have an obligation to ensure the safety of those involved in HPTN research, which includes the obligation to make effective means of prevention available.

***Guidance 3.3: In order to conduct HIV prevention research in settings where standards of care are poor, the HPTN will consider options for contributing to the improvement of the local infrastructure so that the standard of care might be improved.***

Research aimed at identifying effective primary HIV-prevention strategies in resource-poor settings may require a level of clinical monitoring and care that is different from what is normally available in these settings. There are differing opinions as to whether the provision of superior care during research constitutes a benefit only (5) or could constitute undue inducement under some circumstances.(4) Although this issue has been considered largely in terms of its relevance to the individual participant, it has relevance for communities as well. Regardless, these issues arise in large part because of global inequities in access to health care. Consequently, effective resolutions would be those that strike at this immense root cause. Although efforts to reduce this larger issue may be beyond the scope of individual research endeavors, alleviating such disparities ought to be considered as an aspirational goal for HIV prevention research as a whole.

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Given the concerns about the potential for undue inducement to participation due to the provision of care necessary to conduct research, it is incumbent upon investigators to explicitly consider realistic options for dealing with these disparities.

***Guidance 3.4: In designing and conducting its research, the HPTN will explicitly consider the local standards of care, the implications of those standards for research participants, and the potential impact of research-associated care on the local community.***

As a matter of justice, access to care in the local community must be considered with reference to the local context. In addition to the local standard of care, additional services that are not normally available in the local community may be provided directly to HPTN research participants following an assessment of the potential impact of such services on (1) informed consent, (2) equity in local access to care, and (3) local health care priorities. Such an assessment is necessary given that the provision of care that is otherwise not accessible to research participants can result in undue inducement to participate in the research. It is also necessary due to the uncertainties surrounding the community-level implications of introducing dual standards of care.

#### **Section 4. Informed Consent**

***Guidance 4.1: Each HPTN site involved in a research project will develop, document, and implement a meaningful informed consent process unless the research meets accepted criteria for waiving informed consent.***

Informed consent is typically a necessary component of ethically acceptable research. Derived from the ethical principle of respect for persons and the political principle of liberty, it is generally inappropriate to do things to others without their express consent. Meaningful, or valid, informed consent requires that an individual be competent to engage in decision-making about the proposed research and positioned to make a voluntary choice concerning it. If these conditions are met, the individual must be

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provided with sufficient and understandable information about the proposed research and its alternatives to enable a genuine choice. Finally, if the individual decides to participate, this decision needs to be made explicit. In some settings, explicit authorization to proceed occurs through a signature or other personal mark on a consent document. From an ethical perspective, informed consent is only obtained if each of the substantive requirements is met.

***Guidance 4.2: The informed consent process for each HPTN research project will accurately describe the procedures to be followed and the components of care that are to be made available as a result of research participation, including whether access to any or all of those components will be sustained once research participation ends or the research is completed.***

As described above, for informed consent to be meaningful, potential participants need thorough information about the proposed research in a manner that is understandable to them.(8) Although the minimal elements to be included when disclosing information to potential research participants can be found in regulatory materials such as the U.S. regulations codified at 45 CFR 46.116 or the ICH-GCP guidelines, it is critical that those developing informed consent processes and those charged with obtaining it incorporate relevant information. For example, benefits of participation in research include direct, collateral or indirect, and aspirational aspects.(9) Likewise, risks include medical, social, psychological and economic aspects. In communicating this information, it is important to take steps to minimize the “therapeutic misconception” in which potential research participants believe erroneously that interventions being done solely for research purposes are being implemented for their personal benefit.

***Guideline 4.3: The protocol team and each HPTN site involved in a research project will consider the need for continuing consent by participants and establish mechanisms for addressing such needs.***

In order to fully respect the dignity and autonomy of research participants it is necessary to acknowledge that experiences, knowledge acquisition, and understanding necessarily shift over time. For instance, as participants gain experience with research, they may change their minds about participation. If the research continues for extended periods of time they may forget or become confused about aspects of the research or their role in it. Personal circumstances may change such that a reassessment of one's willingness to participate is warranted. Respect for persons also requires full disclosure of new information that could be of material interest to participants with regard to continuing in the research.

## Appendices

### A. Biomedical and Public Health Ethics

Many of the relevant ethical considerations for biomedical research consist of three principles: respect for persons, beneficence, and justice(10). Although some have criticized the adequacy and appropriateness of using these principles to guide ethical decision making for research, they can be quite helpful in describing and analyzing issues and are therefore included as a key part of the framework for this document.

The first principle states that all persons deserve respect and should be treated as autonomous agents; additionally, persons with diminished autonomy are entitled to protection. This principle is commonly implemented via the concept of informed consent. Respect for autonomy “involves acknowledging decision-making rights and enabling persons to act autonomously, whereas disrespect for autonomy involves attitudes and actions that ignore, insult, or demean others’ rights of autonomy” (11)(page 63). Further, “[r]espect for autonomy obligates professionals in health care and research involving human subjects to disclose information, to probe for and ensure understanding and voluntariness, and to foster adequate decision-making” (11)(page 64).

The second principle centers on beneficence and typically encompasses the corollary principle of nonmaleficence. The principle of beneficence “refers to a moral obligation to act for the benefit of others” (11)(page 166) and “provides the primary goal and rationale of medicine and health care”(11) (page 177). The principle of nonmaleficence “requires intentionally refraining from actions that cause harm” (11)(page 115), where harm is construed as “thwarting, defeating, or setting back” a person’s interests (11)(page 116). Together, they denote obligation to ensure both the greatest benefit and the least harm possible, which can entail a careful balancing of risks and benefits.

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The third principle is that of justice, or the obligation to ensure a fair distribution of the risks and benefits of research among participants and within society. The principle of justice minimally requires that the equality of persons be defined in terms of relevant properties, and that persons thus defined as equals in terms of those properties be treated equally(11) (page 227-230). One conception of justice invokes an obligation to ensure fair opportunity such that a person receives “the benefits needed to ameliorate the unfortunate effects of life’s lottery” (11)(page 236).

Though we accept the fundamental importance of these principles as a framework, it is important to note that considerable controversy has emerged in recent years over their interpretation and application in the context of biomedical research, especially that sponsored by wealthy countries in poor country settings. As noted in the previous sections, the ethical challenges for HPTN research are reflected in still evolving, and, at times, contradictory revisions to international documents such as the World Medical Association’s (WMA) *Declaration of Helsinki*(12) and the Council for International Organizations of Medical Sciences’ (CIOMS) *International Ethical Guidelines*.(4) Additionally, many countries have developed or are in the process of developing their own ethical guidelines for research.

There is also movement toward establishing an ethics framework specifically for public health. Mann (13) argued that bioethical principles did not provide a sufficient foundation for public health, defined as “what we, as a society, do collectively to assure the conditions for people to be healthy” (14). He noted that threats to human rights, to human dignity, and to health share common social determinants, suggesting that human rights ideals could provide a pathway for defining a new ethics of public health. In many ways, however, this can be understood as an articulation of the principle of justice. Gostin (15) points out that “the quintessential feature of public health is its concentration on communal well-being, and that this feature separates public health from medicine.” The ethical implications of arguments such as these are only now being explored, despite their obvious relevance for the ethical controversies surrounding HIV prevention

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research. (16-18) HIV prevention research creates both a moral imperative and an opportunity to move the ethical debate forward from the level of the individual participant to one that more completely encompasses both the individual and the community. To accomplish this, we must explore the obligations of researchers and sponsors in local settings and as members of a global research network.

## **B. Ethical Tensions in International Research**

Ethical challenges identified by HPTN members reflect several areas where tensions exist in current ethics guidance. A brief comparison of three recent documents highlights the kinds of ethical decision-making that U.S.-based sponsors and researchers must confront with regard to research conducted in developing countries: (1) the World Medical Association's *Declaration of Helsinki*, revised in October 2000 (referred to hereafter as Helsinki 2000)(12); (2) the January 2002 revised draft of the Council for international Organizations of Medical Sciences' *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS 2002 draft)(19); and (3) the 2001 National Bioethics Advisory Commission report on *Ethical and Policy Issues in International Research* (NBAC international report).(5)

With regard to standards of care for treatment of research participants, Helsinki 2000 unambiguously states that the well being of the research subject must take precedence over the goals of the research (paragraph 5). This standard is premised on the assumption that the research context builds on, and is secondary to, a physician-patient relationship. The CIOMS 2002 draft describes a more complex set of relationships and roles, and does not presume that research will be predicated on an existing physician-patient relationship. The CIOMS 2002 draft states that it is morally praiseworthy to provide care beyond that needed for the research itself, but notes that "medical services [should not be] so extensive as to induce prospective subjects to consent ... against their better judgment" (commentary on Guideline 11). The NBAC international report leans more toward Helsinki 2000 than the CIOMS 2002 draft by arguing that the provision of medical care, by its very nature, cannot and does not create undue inducement to

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participate in clinical trials (pages 46-48). All three documents stress the importance of distinguishing medical care from research during informed consent. But how this is to be accomplished if medical care is available only as a result of the research is not addressed.

The use of placebo controls in clinical trials testing the efficacy of a shortened course of AZT to prevent mother-to-child transmission of HIV in developing countries precipitated the drafting of the documents discussed here.<sup>(20)</sup> The central issue focused on whether use of a placebo control could ever be justified when a treatment of known efficacy exists. Helsinki 2000 made the strongest, clearest statement with regard to this issue, stating that the best current prophylactic method must be used (paragraph 29). The NBAC international report begins with a similar statement then qualifies it by stating that a placebo may be used if it is justifiable to do so (Recommendation 2.2). The CIOMS 2002 draft specifically states that use of a placebo must be scientifically and ethically justified (Guideline 7). In 2001, the World Medical Association published a clarification of their position regarding the use of placebos when a known therapy exists, stating that placebos may be ethically acceptable if there are “compelling and scientifically sound methodological reasons” for their use or if they do not result in additional risk of serious or irreversible harm. However, the *Declaration of Helsinki* has not been modified and the implications of this clarification for application of Helsinki 2000 to decision-making are unclear.

With regard to issues of justice, the CIOMS 2002 draft focuses on the need to ensure a favorable balance of potential benefits and risks (Guideline 4). Helsinki 2000 states that this balance must also include the ability of all research participants to access the best-proven method identified by the research (paragraph 30). The NBAC international report includes a similar, but more specific requirement, that participants should be provided continued access to proven effective experimental interventions (Recommendation 4.1). Helsinki 2000 and the NBAC international report guidelines are thus more likely to require the identification of resources for developing and sustaining health infrastructure beyond that needed for the research itself.

With regard to societal benefits, the three documents take slightly different approaches. Helsinki 2000 requires that the research present a reasonable likelihood of

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benefit for the host country (paragraph 19). The NBAC international report recommends that the research be responsive to the health needs of the host country (Recommendation 1.3). The CIOMS 2002 draft states that the research should be responsive to local health needs and priorities (Guideline 6). On this issue, the CIOMS guidance is most likely to result in limits on the type of research that would be undertaken in developing country settings.

To what extent are researchers from developed countries obligated to enhance the ability of their host countries to conduct research or implement its results? Helsinki 2000 is silent on this issue, perhaps reflecting its primary concern with the physician-patient relationship. Both the NBAC international report and the CIOMS 2002 draft, however, include fairly extensive discussions of this issue and state that capacity building is a necessary component of research in this context. They have clearly shifted the bioethics debate toward consideration of the extent to which science is morally obligated to address inequities in the larger political-economic context of research.

### **C. Ethical Challenges in Conducting HPTN Research**

The HPTN research agenda is carried out within a context of complex social, political, and economic problems that cannot be ignored because they are closely tied to the HIV pandemic and to the shaping of responses to it.(7;21-23) Benatar(24) has argued that “the ethical dilemmas faced in conducting collaborative international research can only be addressed satisfactorily if research ethics is seen as intimately linked to health care, to human health globally and to the promotion of social and economic processes that could begin reversing widening global disparities in health” (p. 1131). HPTN experience provides evidence in support of this perspective. In July 2001 the Ethics Working Group surveyed a wide range of Network members by email to identify the kinds of ethical issues they were confronting. Interviews were also conducted with working group coordinators and other FHI CORE staff. Information was elicited from approximately 25 principal investigators, local site investigators, FHI staff, and other members of science and community working groups. The responses were compiled and the following issues

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identified as crosscutting concerns within the Network, which then formed the basis for this guidance document.

*Establishing Acceptable Shared Standards of Care*

Multisite studies present a major challenge to the HPTN due to the extreme differences in available health care that exist between participating sites, both domestic and international. To what extent should a single protocol require comparable levels of care across all sites? Conversely, a single site may be implementing multiple protocols that differ with regard to the level of care to be provided to research participants. Should attention be given to establishing common standards for care across protocols, or within sites?

HPTN investigators asked for guidance in deciding what level of care should be offered to research participants, and whether such care could constitute unfair inducement to participate in a trial if this care is otherwise unavailable. In those settings where discrepancies exist between stated government policies regarding care and what is actually available, as well as settings where there is substantial variability in access to care based on income, investigators asked how they should define the local standard of care. Some investigators solicited guidance on who should shoulder the burden of elevating the background level of care in resource-poor countries. How much of this burden should fall to a research network like HPTN, and would that burden make much needed research prohibitively expensive? Could the lower cost of conducting research in international settings generate savings that could be used to offset this additional cost?

In most countries where HPTN research takes place the standard of HIV-related health care was reported as extremely low, consisting at best of voluntary HIV counseling and testing services. Almost no care was available for people with AIDS including a general lack of prevention and treatment of opportunistic infections, counseling, nutritional supplementation, or palliative care. Some countries have high standards of care on paper,

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but the care and support specified on paper were not generally available except to those few who could pay. Antiretrovirals are increasingly available in some HPTN settings, but especially in Africa, mainly to those with resources to pay and are often limited to mono or dual therapy, which raises concerns about the emergence of drug resistant strains. The care that is available in many communities is less than what is offered to HPTN research participants, creating a dual standard of care, sometimes even within the same facility. Mounting pressure to provide antiretrovirals to HIV-infected participants in HIV prevention research creates a dilemma if it does not occur in parallel with efforts to improve local access generally.

*Appropriateness of host-country selection*

Emerging guidance, such as that found in the proposed revisions to the CIOMS guidance stating that interventions found to be effective should be made available to those in need of the interventions within the community where the research findings were produced, have troubled many investigators. Experiences to date underscore the fact that the translation of research findings to policy and practice is determined by complex political factors.

HPTN investigators asked for guidance in determining whether research was appropriate to the host countries proposed for implementation. For example, given the current lack of resources in many African HPTN sites, concerns were raised that successful results of a trial designed to evaluate the effectiveness of ART for reducing HIV transmission from infected to uninfected partners may not result in an accessible intervention for research participants or the community in those countries. Alternatively, access to antiretrovirals is likely to increase in the next few years and results of such a trial could provide important data to support increased access. To what extent must the political will to implement experimental interventions be assured before the research goes forward?

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HPTN investigators further asked what their responsibility is to negotiate pre-trial agreements to ensure access to or availability of an experimental intervention and supporting infrastructure, should it prove effective at the conclusion of the trial. They requested guidance on how to negotiate these agreements, with whom and when, and how to factor time and money into research budgets to support pre-trial agreements.

### *Stigma*

A number of issues were raised that were related to HIV/AIDS stigma and the potential for discrimination or other social harms as a result of HPTN research. Some investigators noted that the omission of HIV infected individuals from research with uninfected people could result in a presumption of infection by others in the community. There was concern that this presumption could then result in social isolation, discrimination, or even violence against those excluded. In research where HIV-infected persons are recruited for participation, such as trials to evaluate interventions to reduce mother to child transmission, uninfected persons are often recruited as well in an effort to mask the HIV status of the participants. However, this sometimes results in a presumption of infection for participants who are uninfected. Some investigators noted that participants' involvement in research could become known to others despite efforts to protect confidentiality, and that social harms may result if they become known as HIV-infected or at "high risk" for HIV infection. Women are often particularly vulnerable to stigma and discrimination, and the potential for research to increase women's vulnerability through further reducing male responsibility and involvement in HIV prevention needs to be considered.

### *Ethical authority and accountability*

The question of 'whose ethics' should prevail was raised with regard to conflicting requirements from U.S.-based IRBs and regulatory guidance versus host country ethics committees. For example, researchers at one HPTN African site found themselves struggling to balance U.S. requirements for documentation of informed consent with illiterate participants and local concerns about confidentiality, trust, and autonomy. They

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developed a strategy that involved obtaining the thumbprint of the participant signifying consent and the signature of the staff person who administered the consent verifying that the participant was appropriately gave consent. A second staff member then talked to the participant separately, asked questions to confirm that she understood key elements from the consent, verified that it was the participant's thumbprint on the form, and then signed the consent document as a second witness. This strategy differed from the U.S. standards established for the research, which required the witnessing of the administration and signing of the consent form simultaneously by two people. Situations such as this underscore the need for guidance that is responsive to local culture, norms, and sensitivities as well as U.S.-based requirements, and that facilitates solutions that meet the needs of all stakeholders.

Some HPTN investigators expressed concern about HPTN accountability for ethical decision-making. In the event of public controversy over the ethics of HPTN research, they wanted assurance that the leadership within the Network would respond.

### ***Research design issues***

The research mission of the HPTN is largely driven by the fact that HIV is a global epidemic that mirrors global inequities, as well as by the need to find effective interventions to reduce HIV-related morbidity and mortality at the population level. As such, the HPTN research agenda is derived from public health priorities, rather than clinical care and service priorities. This brings to the forefront the controversial question of when a placebo control arm can be justified.<sup>(20)</sup> For example, if a known effective intervention is not available in the research setting and the goal of the research is to determine whether an experimental intervention would provide a cost-effective option that is better than the existing local standard of no intervention, is use of a placebo control ethically acceptable? Should priority be given to establishing superiority of the intervention to the existing local standard, or to establishing equivalency to a locally non-accessible but proven effective intervention? What if use of a placebo in that setting

would significantly shorten the length of time needed to determine effectiveness of the experimental intervention?

### ***Informed consent***

As described in item 4 above, the development of appropriate procedures for obtaining informed consent presents difficult challenges for HPTN research. The research is often highly complex, the regulatory requirements for documentation are stringent, the cultural settings are highly variable, participants are often illiterate or have limited literacy, those who are literate often lack knowledge of research principles and terminology, and local languages may lack a vocabulary for describing the research. Given the poverty and limited access to health care services that many participants experience, there is also the potential for undue inducement if the consent process inadequately supports autonomy. Guidance is needed for developing an appropriate informed consent process, for ensuring that participants are meaningfully informed and able to make autonomous decisions, and for documenting informed consent in a way that meets regulatory requirements.

### **D. HPTN Ethics Activities**

This guidance document represents one of several efforts undertaken by the HPTN to support ethical decision-making and practice. Members of the EWG have taken leadership on the development of manuscripts that address the ethical dimensions of collaboration and partnership, standards of care, and informed consent within the HPTN context. The EWG has also established a subcommittee that is evaluating the need for ethics training and capacity building and developing a set of recommendations for addressing that need. Initial plans for the establishment of a database of potential ethics consultants have been discussed. Other activities that will be required to support implementation of this guidance include the development of ethics checklists for use during CORE site monitoring.

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