HPTN
HIV Prevention
Trials Network

HPTN

Ethics Guidance for Research

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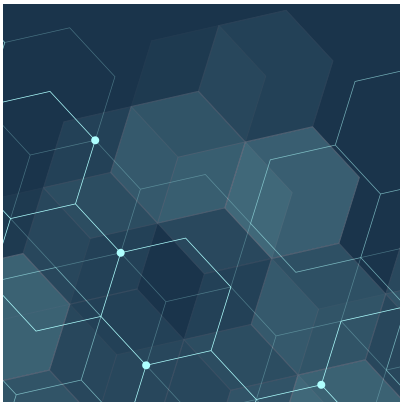

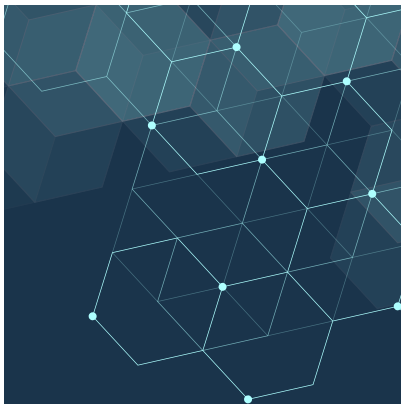

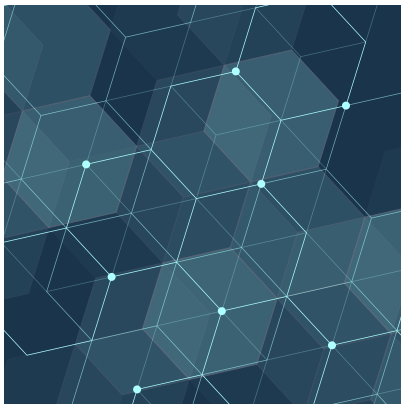

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LIST OF ABBREVIATIONS

ART:	antiretroviral therapy
AVAC:	AIDS Vaccine Advocacy Coalition
CAB:	community advisory board
CAG:	community advisory group
CD4:	Cluster of Differentiation 4 cells (also known as T helper cells)
CFR:	Code of Federal Regulations
CIOMS:	Council of International Organizations of Medical Sciences
CLIA:	Clinical Laboratory Improvement Amendments
DSMB:	data and safety monitoring board
FTC:	emtricitabine
GPP:	good participatory practices
HANC:	Office of HIV/AIDS Network Coordination
HIV:	human immunodeficiency virus
HPTN:	HIV Prevention Trials Network
IRB:	institutional review board
LARC:	long-acting reversible contraception
MSM:	men who have sex with men
NASEM:	National Academies of Sciences, Engineering, and Medicine
PI:	principal investigator
PrEP:	pre-exposure prophylaxis
PTA:	post-trial access
PWID:	people who inject drugs
PWUD:	people who use drugs
REC:	research ethics committee
SGM:	sexual and gender minorities
sIRB	single institutional review board
SOP:	standard operating procedures
STI:	sexually transmitted infection
US:	United States
TDF:	tenofovir disoproxil fumarate
UNAIDS:	The Joint United Nations Programme on HIV and AIDS
WHO:	The World Health Organization

INTRODUCTION

The human immunodeficiency virus (HIV) epidemic persists: There are nearly two million new infections reported each year and the global burden of disease is increasing (UNAIDS 2018). Morbidity rates from HIV have increased in resource constrained settings despite enhanced access to antiretroviral therapy (ART) in many parts of the world (UNAIDS 2018). From a scientific and public health perspective, research on HIV acquisition and transmission should focus primarily on communities and groups with high HIV incidence. However, the design and conduct of such research introduces ethical challenges, particularly in settings marked by poverty, laws affecting key populations, weak health care infrastructures, inequality, discrimination and stigma.

The HIV Prevention Trials Network (HPTN) is a worldwide collaborative clinical trials network that brings together researchers, community members, ethicists and other partners to develop and test the safety and efficacy of interventions designed to prevent the acquisition and transmission of HIV. Building on the work of the HIV Network for Prevention Trials, between 1999-2019 alone, the HPTN conducted nearly 70 HIV prevention clinical trials in 20 countries and over 80 research sites.

This ethics guidance document aims to raise awareness of the ethical considerations associated with HIV prevention research, engage all HIV prevention stakeholders in discussion about those considerations, and facilitate the integration of ethical considerations and the highest ethical standards of practice into the design and implementation of HIV prevention research. Although there are other ethics guidance documents for research in general and HIV-related research in particular, this guidance is intended to offer a practical approach to identifying and addressing ethical issues in the practice of HIV prevention research that is sensitive to the sometimes competing claims of policies and other normative documents. While HIV prevention research is typically subject to procedural review by official bodies (e.g., drug regulatory agencies, government ministries, and ethics review boards), such processes are related to, but distinct from, ethics guidance that aims primarily to facilitate the design and conduct of research consistent with fundamental ethical principles.

Context

In 2003, the HPTN Ethics Working Group developed the *HPTN Ethics Guidance for Research* (MacQueen et al. 2003), which was subsequently updated in 2009 (Rennie and Sugarman 2010).

Several developments over the last decade have prompted this revision of the document:

- **Advances in HIV prevention science**: Advances in HIV prevention science, most prominently the demonstrated efficacy of treatment as prevention (Cohen et al. 2016) and oral pre-exposure prophylaxis (PrEP) (Grant et al. 2010, Baeten et al. 2012, WHO 2015, FDA 2019), introduce ethical complexities in the design of HIV prevention trials, especially as access to these interventions increases.

- **Research priorities and responsiveness**: Increased emphasis is being placed on the importance of answering research questions that are locally relevant and responsive to host communities' health priorities, including guidance on how best to do so (UNAIDS/WHO 2012, Shah et al. 2013, CIOMS 2016, Wenner 2017).

- **Community engagement and capacity-strengthening guidance**: Multiple guidance documents have emerged that specify how to engage communities in particular contexts and broaden the scope of strengthening local capacity beyond healthcare and the conduct of research (Weijer et al. 1999, UNAIDS/AVAC 2011, UNAIDS/WHO 2012, UNAIDS/WHO 2013, HANC 2014b, HANC 2014a, CIOMS 2016, Baron et al. 2018, MacQueen and Auerbach 2018).

- **Evolving guidelines, policies and regulations**: Several important guidelines, policies and regulations have evolved. For example, the updated Council of International Organizations of Medical Sciences (CIOMS) (2016) guidelines place greater importance on the scientific and social value of research, aim to include vulnerable populations, and address concerns with the traditional informed consent process. The latest version of the Declaration of Helsinki emphasizes the importance of minimizing risks and burden to research participants, considering arrangements for post-trial continuation of beneficial study interventions, establishing privacy protections, assessing capability of giving informed consent, providing study results to participants, and distinguishing care from research (World Medical Association 2013). The revised Common Rule in the United States (US), which is relevant for those who receive US federal funding for research, includes provisions related to broad consent and biospecimens (45 CFR 46.116) and requires single committee review (i.e., by an Institutional Review Board (IRB) in the US) for domestic multisite studies (45 CFR 46.114.b.1).

- **Disseminating research results**: Standards have changed regarding access to and dissemination of research results, such as providing participants with lab or health-related results and information about the arm of the study to which they were assigned, and third parties with access to raw datasets (Dinnett et al. 2005, Peat et al. 2014, Boué et al. 2018, NASEM 2018).

- **Post-trial access**: HPTN stakeholders and others have published empirically-derived guidance on how to implement plans regarding post-trial access (PTA) to successful interventions (MRCT 2017, Paul et al. 2018).

- **Advances in genomics and molecular phylogenetics**: Molecular epidemiology is playing an increasing role in HIV prevention research but raises ethical, legal, and social issues related to determining directionality of HIV transmission that could result in stigma, discrimination and criminal prosecution (Coltart et al. 2018).

Goals and audience

MAJOR GOALS OF THE HPTN ETHICS GUIDANCE DOCUMENT:

- Provide useful and practical guidance for addressing ethical challenges in HIV prevention research, including clinical trials, behavioral studies, implementation research and community-based trials.
- Address gaps, limitations and inconsistencies in existing ethics guidance relevant to HIV prevention research.
- Articulate the ethical responsibilities of key stakeholders involved in HIV prevention research.
- Describe ethical challenges arising in the design and conduct of HIV prevention research.
- Contribute to local ethics capacity-strengthening at HIV prevention research sites and foster a culture of ethical responsibility among HIV prevention researchers.

Ethical decision-making in research requires a deliberative process. No guidance document, including this one, can eliminate the need to identify relevant issues and then engage in a process to describe, analyze, and balance the ethical tensions inherent in every situation. Nevertheless, this guidance aims to help ensure that ethical decision-making regarding HIV prevention research is of the highest quality, despite prevailing uncertainties and the pressure to generate short-term responses to complex, long-term problems.

This guidance document draws on the extensive experience of the HPTN, which conducts international HIV prevention research that prioritizes and integrates ethics through all phases of the research process. Earlier versions of the guidance document were designed to help the HPTN

define and meet its ethical obligations, and the HPTN and other HIV prevention researchers continue to be the primary audience. For researchers, the guidance is designed to facilitate discussions and ethical decision-making regarding the development and implementation of research objectives and protocols. However, the guidance has since had, and aims to have, wider applications for the HIV prevention research field at large.

Collaborating institutions/organizations, community members and community representatives constitute another audience, as does the wider group of stakeholders involved in or affected by HIV prevention research activities, which can include government representatives and agencies, pharmaceutical companies and other industry sponsors, non-governmental organizations, HIV/AIDS activist groups, and ethics and scientific review committees.

The hope is that the guidance will also continue to contribute to discussions surrounding the ethical aspects of HIV prevention research and will help other groups and agencies conducting similar research.

Organization and approach

This ethics guidance document is organized roughly according to the different stages of HIV prevention research, from preparation through implementation and activities after completion of the data collection phase. Each research stage has its own set of ethical considerations. This document identifies the primary stakeholder(s) who are responsible for implementing each of the described ethics guidance points.

Not all ethics points that are stated in the guidance are of equal strength or significance. There are important differences between those that express ethical obligations versus those that pertain to ethical aspirations. If a course of action is described as an **ethical obligation** (such as 'should', 'must' or 'will'), then normally the action should be performed; while exceptions to that course of action are sometimes permissible, they require a strong ethical justification. For example, obtaining informed consent is an ethical obligation, but there may be cases in which consent can justifiably be waived (see Guidance Point 6). In contrast, if a course of action is expressed as an **ethical aspiration** (such as 'strive to' and 'making good faith efforts') this implies that the course of action is a matter of pursuing important ethical ideals and is desirable, but not required. Regardless, in general, all stakeholders in HIV prevention research are encouraged to fulfill their ethical obligations and to pursue ethical aspirations to the greatest extent possible.

The HPTN ethics guidance document is distinguished from other existing guidance in three ways. First, the HPTN guidance is grounded in significant experience arising from the design and implementation of HIV prevention research. Second, the guidance document recognizes that ethical aspirations will have a meaningful impact only if they can be applied to actual research settings in which political, social, economic, cultural and regulatory constraints and challenges are

routinely encountered. Third, the guidance aims to distinguish different strengths of ethical requirements and identify those who are primarily responsible and accountable for fulfilling them.

Fundamental ethical principles in research

The design and implementation of HIV prevention research should be grounded in the following fundamental ethical principles:

Respect for persons

Respect for persons entails not only respecting the decisions participants make in the context of research, but also helping to empower their decision-making, particularly for those with diminished capacity and/or autonomy. In addition, it captures the obligation to protect participants from the invasion of privacy and bodily integrity.

In respecting persons, researchers must consider the cultural values of the community in which research takes place and protect the community from potential harm where possible. This is sometimes referred to as respect for communities. Research takes place within communities whose ways of life, beliefs, institutions and customs are typically deep-rooted, valued and meaningful to its members. Utilizing good participatory practices demonstrates respect and can help enhance the scientific and ethical quality of research. Obtaining prior 'community assent' for research activities may be regarded as an appropriate expression of respect for the community in some circumstances. This will vary relative to the cohesion of the community (Weijer et al. 1999).

Beneficence

There is the fundamental obligation that research should be designed in such a way as to minimize potential risks of harm to participants and to provide substantive benefits to them where possible. The risks should be understood broadly to include physical, psychological, legal, social and economic risks for both individuals and communities. Research designs must anticipate risks and incorporate benefits on the basis of the best available scientific knowledge and community engagement. Risks should also be justified by the social value of the research, which may include direct or future societal benefits.

Justice

The concept of justice has many meanings. For the purposes of this document, the term expresses the ethical concerns related to treating people fairly, avoiding exploitation, and trying to reduce health disparities. This captures the need for fair selection of participants as well as broader concerns. Of note, there are vast inequalities in health, income, and power between and within countries worldwide. In such settings, researchers are challenged to improve health without taking unfair advantage of, or increasing, existing social inequities. To the extent that it is reasonably possible, researchers and other stakeholders should seek to reduce social inequalities and inequities in the domains of health and health care by, for example, developing local health-related capacity and reducing stigma.

ETHICS GUIDANCE POINTS

GUIDANCE POINT 1. HIGH-QUALITY SCIENTIFIC AND ETHICAL RESEARCH

Those engaged in HIV prevention research must be committed to designing and implementing high-quality scientific research and research ethics practices throughout the research process.

- ***Status:*** Ethical obligation
- ***Responsible and accountable:*** Sponsors and researchers

Scientifically sound research

Sponsors and researchers have primary responsibility to ensure the HIV prevention research is scientifically sound. A formal review process should be undertaken to help ensure that HIV prevention research meets the highest scientific standards. In addition, researchers should conduct formative research, if necessary, to validate measures and data collection strategies, mitigate potential harms, make study procedures context-specific, and ensure that the research is locally relevant.

Ethically sound research

Ethically sound design and implementation of research requires thoughtful interpretation of ethical principles in local contexts. For internationally collaborative HIV prevention research, this can also require the careful balancing of disparate local realities at multiple research sites, such as stigma, policies and law enforcement practices. Ethical evaluation at key points in the research design and implementation process should help to ensure that ethical considerations are addressed in tandem with scientific and logistical considerations. The following steps help to ensure that ethical considerations are addressed, recognizing that this research will also undergo review by the responsible IRBs or research ethics committees (RECs) established under US and collaborating country regulations (See Guidance Point 8):

- ***Research concepts***: A new research concept or proposal should include a brief statement that identifies key ethical considerations associated with the proposed research. Researchers are encouraged -- but not required -- to obtain input from those with expertise in research ethics in the earliest stages of development of research concepts to help ensure that ethical challenges are recognized and addressed.

- ***Protocol development***: Researchers are ethically obligated to involve host country stakeholders, including local researchers, community advisory boards or other community representatives, as early as possible in the protocol development process to ensure responsiveness of proposed research to local health priorities and community values (see Guidance Points 2 and 3). If possible, ethics expertise should also be included on the protocol team to help address the ethical challenges.

- ***Protocol review***: If a protocol technical review process is required (independent of IRB/REC review), an ethics reviewer with appropriate expertise in HIV prevention research should be designated. This is standard practice in the HPTN. To avoid potential biases or conflicts of interest, persons who have served either as members of the study team or as consultants to it should not serve as ethics reviewers for that protocol.

- ***Protocol implementation***: Research operations manuals or standard operating procedures (SOPs) should address standard ethics domains (e.g., informed consent procedures) as well as any special ethical concerns that are identified during protocol development and approval. Study assessment activities should include attention to ethical concerns identified during protocol development. Research staff should consult with ethicists to develop checklists or other measures to facilitate assessments, such as the evaluation of potential participants' understanding during the consent processes. Assessment of ethics-related activities should complement monitoring for compliance with regulatory requirements for human subjects protections performed by approved monitors.

GUIDANCE POINT 2. RESEARCH OBJECTIVES AND PRIORITIES

HIV prevention research should prioritize efforts that address public health needs, reduce health inequities, and are locally relevant.

- ***Status:*** Ethical obligation
- ***Responsible and accountable:*** Sponsors and researchers

Health research that fails to respond to a local health priority, and is hence unlikely to produce any significant benefit to local communities, can be exploitative. HIV prevention researchers should focus their efforts on research questions that are responsive to local health priorities (CIOMS 2016) and address health deficits, but which also have scientific value and potential global relevance for curtailing the HIV/AIDS epidemic. Ensuring that research is responsive to local health priorities helps protect host communities from exploitation (Wenner 2017) and enables them to benefit (Grady 2006).

While HIV prevention is a global health priority, not all HIV prevention research addresses local priorities, even when conducted in countries of high HIV incidence. To ensure a non-exploitative and equitable exchange between sponsors, researchers and host communities, the benefits that are reasonably expected to emanate from research responsiveness should be evaluated on a study-by-study basis in regard to the host community's priorities and needs (Grady 2006, Shah et al. 2013). Responsiveness necessitates respecting the authority and informed input of host communities to prioritize their own health research interests (Wenner 2017). Determination of the extent to which a particular HIV prevention research activity or study responds to a local health priority should be undertaken by drawing on available sources. These include surveillance data, results of prior public health and behavioral research, government reports, and consultations with stakeholders including representatives of local health departments or the Ministries of Health (UNAIDS/WHO 2012).

The major ethical concern is that, in the absence of relevance to local needs, research may be disconnected from local health priorities such that the information obtained and/or intervention proven by the research may not benefit the community where the research is performed. If an intervention were deemed to be inappropriate or infeasible for adoption within a reasonable time horizon even if proven safe and effective in a community participating in the trial, or similarly if the information could not be usefully integrated in local health systems, it may not be ethical to conduct the trial at that site.

GUIDANCE POINT 3. COMMUNITY ENGAGEMENT

Relevant communities should be actively engaged throughout the research process to help ensure that HIV prevention research is appropriate as well as scientifically and ethically sound.

- ***Status:*** Ethical obligation
- ***Responsible and accountable:*** Researchers, study teams, and community representatives

Engaging with, listening to, and recognizing the autonomy of communities early in protocol development and throughout the research process demonstrates respect for communities. Failure to demonstrate such respect may undermine the ability to conduct and complete important HIV prevention research.

HIV prevention researchers should outline steps to develop, maintain, and support meaningful participation of relevant community stakeholders in all phases of the research process. This includes plans for education and training, communication, and 'crisis' management. The extent of community engagement should be tailored to the type, stage, length of the proposed research, and the potential risks to participants; less extensive community engagement may be justified for small studies of short duration and minimal risk. However, when conducting research with extremely disadvantaged or stigmatized populations/communities, such as men who have sex with men (MSM) in countries where same sex activity is criminalized, and people who inject drugs (PWID) in countries where drug use and harm reduction is criminalized, the ethical obligation to engage deeply with these communities increases because of the very real potential for serious social harms. Researchers conducting research in these contexts need to be particularly responsive to the perspectives of representatives of marginalized communities (Haire and Kaldor 2018). In addition, HIV prevention researchers should involve local community representatives as early as possible in discussions about the use of biospecimens. Nonetheless, formative research may be warranted to identify and respond appropriately to possible rumors and misconceptions surrounding collection of human tissue or other aspects of the research including product design.

Meaningful community engagement generally requires a two-way learning process for community stakeholders and researchers. Community stakeholders may be unfamiliar with some scientific concepts, while researchers may lack the language skills, cultural background and experience to identify and appreciate community concerns about research. In many settings, researchers should acknowledge and address historically-grounded mistrust of biomedical research (Newman et al. 2015). In order to enhance two-way learning, research leadership and research teams should be appropriately diverse to reflect the proposed study population, particularly when a study targets specific social, ethnic or racial groups (e.g., Black men in the US, immigrants, sex workers), and sexual and gender minorities (e.g., gay, two-spirit, bisexual, transgender, intersexual).

The term 'community' can carry different meanings in different settings and, as a result, may be difficult to translate across languages. The way 'community' is defined has implications for who is included in, or excluded from, the research engagement process. The *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials* (GPP) recommends use of the term *community stakeholders* to mean "both individuals and groups that are ultimately representing the interests of people who would be recruited to or participate in a trial, and others locally affected by a trial" (UNAIDS/AVAC 2011).

Dealing with HIV-related stigma through product design

In HIV prevention trials involving the use tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) PrEP, some participants reported that they were compelled to keep their use of the study product a secret because others in their communities recognized the distinct tablets as a treatment for HIV infection. Participants were concerned that others would assume they were infected, and they would then be subject to HIV stigma and discrimination; indeed, some participants reported such harms from sex partners, family members, friends and employers. Participants who felt a need for secrecy around product use often found it harder to be fully adherent, which in some studies contributed to futility and early trial closure. Because packaging is part of the research design and regulatory approval process for clinical trials, it cannot be modified midstream. The potential for product-related stigma needs to be addressed early in designing research. Formative research during the protocol development phase offers an opportunity to inform the development of a product form and packaging that is non-stigmatizing, supportive of adherence, and acceptable for regulatory purposes. (van der Straten et al. 2014, Montgomery et al. 2015, Corneli et al. 2016, Franks et al. 2018, Montgomery et al. 2019).

For HIV prevention research, community stakeholders may include:

- Parents, children, spouses, siblings, caregivers, sexual partners, and other significant relations of research participants;
- The group from which research participants will come (e.g., persons at risk for HIV who use services in a prenatal clinic, transgender women living with HIV, PWID in a certain location, or a geographic community);
- Those living in the geographic area in which the research will be conducted; and,
- Influential or key individuals from the area in which the research will be conducted (e.g., traditional, religious or governmental leaders, professionals or volunteers who work with local HIV prevention or research programs, and members of the health care and medical workforce).

GPP distinguishes community stakeholders from broader trial stakeholder groups including "trial funders, sponsors, and implementers, as well as government bodies or representatives of high-level authority structures" (UNAIDS/AVAC 2011). Researchers should begin community stakeholder engagement efforts as early as possible in the research development process, including the formulation of research questions if feasible. Early engagement of stakeholders helps build a foundation of trust through shared learning, transparency, and accountability (MacQueen and Cates 2005, MacQueen and Auerbach 2018).

The principal investigator (PI) at each site should ensure that relationships with community stakeholders are maintained. PIs should support involvement and participation of community stakeholders in research planning and ensure that information about concepts, protocols, and research is provided in ways that are accessible and appropriate for community stakeholders. Community ideas and concerns should be taken into account. All research staff share responsibility for community stakeholder engagement to varying degrees; however, dedicated community engagement staff with appropriate training, skills and experience may be needed to plan and implement engagement activities.

For large-scale or especially risky research, an advisory mechanism should be established at each site to engage community stakeholders, with the most common approach being the creation and maintenance of a Community Advisory Board or Group (CAB or CAG). The advisory structure at each site should be responsive to local needs and context. Community representatives should be credible and legitimate, and selected by the research team after consultation and screening with key community stakeholders.

Appropriate representatives will vary from site to site depending on local needs and context, but may include representatives of relevant non-governmental organizations, persons living with HIV, community leaders (such as teachers or religious leaders), health care professionals, and persons in the community likely to benefit in the future from the tested intervention should it be found to be effective and safe. Expectations for CAB/CAG member engagement and activities should be defined, and the research team should preserve the ability to replace CAB/CAG members who appear not to be authentically representing the affected community/ies.

Addressing stigma in referrals to care for sexual and gender minorities

Referrals for care to settings that stigmatize sexual and gender minorities (SGM) can result in their not accessing such services or receiving substandard treatment, perhaps resulting in social harms (e.g., blackmail, arrest). This highlights the need for research teams to understand how stigma is experienced by SGM in local health care settings. SGM members should have a seat on CAB/CAGs and have a voice in the decisions about where referrals are made and help to identify additional sites for safe referrals. With their active participation, a research team can vet referral sites in person, determine if the health care site is welcoming and capable of providing services for SGM, and arrange to provide training on health care delivery for SGM if needed. Through this process, research sites may identify some SGM health care needs that cannot be adequately met in the local community and may need to plan to provide that care directly for SGM participants (Fay et al. 2011, Kennedy et al. 2013, Arreola et al. 2015).

CABs/CAGs should provide advice on scientific and ethical issues such as study design and recruitment, as well as the protection of participants. These representatives are important intermediaries between researchers and community stakeholders and should convey advice, concerns, beliefs, and norms to site staff. In their capacity as community representatives, they should put community goals before personal goals, strive to ensure that all significant perspectives are raised (including views of community members or groups that may differ from their own) and help mediate potential disputes among community groups. The responsibilities of CAB/CAG members can be demanding, and due consideration should be given to how those responsibilities are compensated while maintaining CAB/CAG independence and autonomy. Although it is critical to engage community stakeholders, HIV prevention researchers should not limit engagement efforts to local community stakeholders, but also attempt to engage other relevant stakeholders. These may include representatives of the agencies and organizations most affected by the trial results such as regional or national policymakers and program implementers.

Researchers and community stakeholder representatives should be aware of various guidelines that have been developed regarding community engagement in HIV research such as:

- Guidance from the American Foundation for AIDS Research, provides information about community engagement in the context of HIV research with gay, bisexual, and other men who have sex with men in rights-constrained environments, including lessons learned, successes, and challenges (amfAR 2015).
- The University of KwaZulu-Natal, South Africa in collaboration with the AIDS Vaccine Advocacy Coalition (AVAC) offer an interactive, online, free, self-paced, certificate-generating, course on Strengthening Stakeholder Engagement through Ethics Review. With a focus on HIV prevention trials, the course provides a condensed overview of core features and practices of engaged research and how these can be highlighted through the ethics review process. It is available through AVAC's Engage platform (https://engage.avac.org/). In addition, there is a GPP Online Training Course which is a hands-on eLearning experience with interactive online content, case studies, work assignments and online discussions (https://www.avac.org/gpp-online-training-course).
- Guidelines from the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO) describe best practices for community engagement and establishment of collaborative partnerships (CIOMS 2016).
- The Office of HIV/AIDS Network Coordination (HANC) details recommendations for community engagement in HIV/AIDS research that delineate important details regarding the creation and use of CABs, such as the roles and responsibilities of the CAB and their support needs (HANC 2014b).
- HANC has also offered guidance for engaging Native American communities in HIV research. The guidance includes useful information about cultural humility training, an example of a successful community engagement model, and the challenges associated with recruiting Native American community consultants (HANC 2014a).
- The Joint United Nations Programme on HIV and AIDS (UNAIDS)/AVAC's GPP provide guidance on relationships among a study's funders, sponsors, and implementers. The GPP describes specific engagement activities that occur at each stage of the research process (UNAIDS/AVAC 2011).
- While it does not solely focus on research, UNAIDS/WHO's guidance on the ethical issues in HIV surveillance provides useful information about community consultation in the consent process (UNAIDS/WHO 2013).

GUIDANCE POINT 4. LOCAL CAPACITY AND PARTNERSHIPS

HIV prevention research should seek to develop local capacity and establish collaborative partnerships.

- ***Status:*** Ethical aspiration
- ***Responsible and accountable:*** Sponsors, researchers, study team, and research sites

Having a locally relevant research objective is only one aspect of research being responsive to local needs. For research to be more broadly responsive, it is ideally part of a larger effort to expand the capacity of health-related social structures in the host community in order to meet its most urgent health needs (London and Kimmelman 2008). Infrastructure development is ideally undertaken in ways that make it likely that it is transferrable to local personnel who have obtained the appropriate training to use it. Examples of transferrable infrastructure include lab equipment and technical training for Cluster of Differentiation 4 cells (CD4) and viral load testing for host country ART program use and expanded lab support for sexually transmitted infection (STI) management (e.g., syphilis serology, vaginal microscopy, gonorrhea culture). Ideally the local lab should be capable of meeting relevant regulatory requirements for clinical research. HIV prevention researchers engaged in research involving the collection of biospecimens should, as part of strengthening local capacity, make reasonable efforts to contribute to local capacity in regard to storage and analyses of biospecimens. Such efforts may also be necessary in terms of research feasibility since the export of biospecimens can be hindered or altogether prevented by laws and practices in some jurisdictions. Nonetheless, building local capacity also includes opportunities for local researchers to participate in the design and conduct of HIV prevention studies through scientific exchange and skills transfer in behavioral and clinical research methods, setting up fair terms of collaborations, and participation in the dissemination of research results to the scientific community. Finally, there may be opportunities to strengthen local capacity in national and local research ethics review.

Development of collaborative partnerships is critical to building and sustaining local capacity. For example, HIV prevention researchers may seek support for transfer of clinical and laboratory infrastructure through partnerships with development aid sponsors and/or local government agencies. For sites that participate in multiple research projects over time, it is especially important to retain research staff and their expertise. Longstanding collaborations between sponsors, researchers, and other stakeholders can facilitate the education and training of individuals who can be employed and function as principal investigators, researchers, assistants, coordinators, and data managers (CIOMS 2016).

Capacity-strengthening is best achieved through early, transparent, and inclusive negotiations among researchers, community representatives, sponsors and other stakeholders. Such negotiations can help develop reasonable expectations based upon an assessment of local needs while acknowledging the primary missions of research funding agencies. Developing creative approaches for capacity-strengthening efforts and seeking alternative sources of support for them are reasonable steps following negotiation.

The aspiration to contribute to local capacity-strengthening is based on the principle of justice. There are often significant disparities in economic wealth, scientific expertise and technical skills between stakeholders involved in HIV prevention research. Given that the desired relationship between external researchers, local researchers and communities is one of collaboration among equals, local capacity-strengthening aims to empower local sites and communities to function as equal partners in decision-making processes surrounding HIV prevention trials (RFI 2018).

GUIDANCE POINT 5. STUDY DESIGN

HIV prevention research should be designed to minimize risks and maximize benefits to study participants and their communities, while remaining scientifically sound.

- ***Status:*** Ethical obligation
- ***Responsible and accountable:*** Researchers and sponsors

Aspects of HIV prevention research design that raise particularly important ethical issues include: (1) early phase research; (2) control and comparison groups in efficacy trials; (3) innovative designs; (4) use of emerging technologies; (5) inclusion of special populations (children and adolescents, women of reproductive age); and (6) responsibilities towards bystanders.

Early phase research

Early phase trials must always be based on sound pre-clinical data. However, they rarely provide any direct benefits to participants and in some cases may expose them to significant risks. Economically disadvantaged participants may join such trials to access ancillary health benefits or monetary incentives that would otherwise be unavailable to them. While protection of vulnerable populations is an important consideration, conducting safety trials in resource-poor settings may be ethically justified. For example, the intervention that is being tested may be directed towards a strain of HIV that is only prevalent in resource-poor countries. A community with high HIV incidence and prevalence may also want phase I/II trials to take place among its population, perhaps as a means of responding to a public health crisis or building infrastructure for a phase III

trial with the hope of eventual access to a successful trial product. However, the conduct of phase I/II trials with vulnerable community members should be scrutinized carefully and the reasons for it substantiated. Researchers must avoid conveying the impression that access to trial products constitutes a benefit of the research since the safety and efficacy of the product under study is not yet known. In addition, the use of placebos in early phase HIV vaccine research, which has been the norm, are not always appropriate on ethical grounds (Huang et al. 2015) and should be explicitly justified in study protocols.

Control and comparison groups in efficacy trials

The use of control and comparison groups in HIV prevention efficacy trials is generally necessary to ensure scientifically valid data are generated, but they may be ethically controversial, particularly in regard to placebo control groups. In efficacy trials, there is generally compelling scientific and ethical justification to include control arms. For HIV prevention efficacy trials, the selection of control arms must reflect accepted practices in HIV prevention while concurrently permitting the generation of scientifically valid results and high quality scientific evidence. A prescriptive approach to the design of control or comparison arms may not be feasible due to the complexity of the issue. However, there should be clinical equipoise regarding each arm of a trial, and interventions tested in HIV prevention studies should generally be compared against interventions known to be effective in the study setting. Any exceptions to these expectations require stringent scientific and ethical justification.

Although there are now safe and effective methods to prevent HIV infection (e.g., oral PrEP), there is still a need to expand the range of available prevention options, which raises questions about the acceptability of enrolling participants for whom current proven methods may not be acceptable (due to a medical contraindication, dislike of the prevention modality, behavioral barriers or concerns about stigma or social harms) in placebo-controlled trials of new methods (Sugarman et al. 2019). Potential participants in such a trial should determine acceptability and usability of a proven prevention product under optimal circumstances before deciding whether to participate in a placebo-controlled randomized clinical trial of an experimental product. Methods to ensure acceptability should be developed with robust community engagement.

In general, proposed research designs must include consideration of the following questions in regard to selecting a control arm (active or placebo):

- Are there other known effective interventions that could be feasibly implemented at the study site to achieve the same goal? Will the experimental intervention be evaluated relative to those interventions? If not, why not?

- Does the trial design preclude or limit the use of any known effective interventions that are or could be made readily available to research participants in the proposed research sites? If so, what are the potential implications for participants?

- If other known effective interventions exist, is there evidence to suggest that the experimental intervention will be more efficacious, cost effective, or socially appropriate to implement in the research communities should the research demonstrate the experimental intervention to be meaningfully effective?

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

Innovative study designs

Innovative study designs are aimed at producing valuable data with fewer resources and reduced risks to participants. Innovative design modalities that are currently being explored include:

- Adaptive designs: Interim analyses of data accumulating in the trial are used to modify the trial's course while maintaining the validity and integrity of the trial (Pallmann et al. 2018).

- Trials using "master protocols": A trial design strategy that tests multiple different drugs/vaccines with a single control arm (Woodcock and LaVange 2017).

- Delayed access or stepped wedge design: A new intervention is rolled-out sequentially and randomly to participants (delayed access) or clusters (stepped wedge) over time and compared to the existing standard of care. By the end of the trial, all individuals or groups will have received the intervention (Mugwanya et al. 2018) although there are some exceptions (Doussau and Grady 2016).

- Surrogate outcome measures: Since there are no reliable markers available to serve as a surrogate endpoint, HIV prevention effectiveness trials now use HIV infection as a clinical endpoint. This has practical and ethical implications. Since HIV infection is a relatively rare event in most settings, prevention studies with this clinical endpoint must enroll a very large number of subjects over a considerable time period. Testing the efficacy of the intervention depends on some participants becoming HIV infected during the period when they are involved in the research. A valid surrogate outcome is therefore desirable. However, it is essential that such surrogate outcome measures are reliable and valid so that the trial will be informative, research resources are used responsibly, and research participants are not unnecessarily exposed to risk.

Each of these designs can raise unique scientific and ethical issues that are beyond the scope of this document to explore, but if they are being considered for use they must be comprehensively and explicitly addressed during the planning stages of research.

Use of emerging technologies

Emerging technologies promise to strengthen HIV prevention research efforts. These include the use of molecular phylogeny and the analyses of large databases as well as a range of electronic platforms and tools.

Molecular phylogeny and big data

- **Molecular phylogeny:** HIV sequence data have contributed to the interpretation of the findings in HIV prevention research, for example by determining whether transmission of HIV resulted from known partners who were being treated for HIV infection in HPTN 052 (Eshleman et al. 2011). In addition, phylogenetic methods are being used to assess how HIV spreads, allowing for better tracking of HIV cases (Leitner and Romero-Severson 2018). As a result, such methods will likely be incorporated into future HIV prevention trials. Responsible implementation of phylogenetic analyses requires: risk and benefit assessments; protection of participants; local social and legal context; risk mitigation strategies to protect identities; valid informed consent; community engagement; communication; and equitable data sharing (Coltart et al. 2018, Fisher and Layman 2018). While some of these requirements are relevant for much research in general, for HIV-related phylogeny research there are special challenges regarding the appropriate uses of data across domains of clinical care, public health and research. In addition, if directionality of transmission is inferred there could be substantial legal and social implications for participants.

- **Big data:** There is increasing use of 'big data' for epidemiological purposes, including HIV epidemiology. A wide variety of extremely large volumes of data can be compiled and analyzed in real-time, often using algorithms without human intervention, in ways that can inform surveillance and intervention activities. For example, HIV prediction models that utilize big data from electronic health records and social media can identify people at high risk of HIV who might benefit from oral PrEP (Young et al. 2017, Krakower et al. 2019, Marcus et al. 2019). Despite the potential benefits of big data for HIV prevention research, it can raise risks of unwanted disclosure of risk behaviors or HIV status, as data may be linked from disparate sources about a particular individual (Mooney et al. 2015, Vayena et al. 2015). This is particularly problematic due to HIV-related stigma and sometimes criminalized behaviors that can be associated with it.

Electronic tools and platforms

Electronic tools and platforms that are or will likely become commonplace in HIV prevention

research as part of interventions, study design, study implementation, data collection, and dissemination include:

- **Texting:** Text reminders have been shown to contribute to HIV prevention. In particular, studies have shown texting to be associated with appointment adherence and uptake of HIV testing (Taylor et al. 2019).

- **Wearables:** Current studies are using wearable sensors that can monitor PrEP uptake, medication adherence, and rapid detection of HIV-1 DNA (Kong et al. 2019).

- **GPS and Social Media:** Global positioning systems (GPS) on mobile phones and computers have been used in social and sexual networking applications to locate other users in the same proximity. HIV prevention interventions have been integrated among some of the more popular applications, which partners use to meet and where individuals may have questions related to sexual health and HIV (Jenkins Hall et al. 2017).

In aggregate, the use of these electronic tools and platforms can raise ethical questions related to ensuring the authenticity of the recipient (e.g., is the person receiving or responding to a text message actually the participant) and privacy concerns of the participant (e.g., inadvertent disclosure of trial enrollment, HIV risk factors and stigmatized behaviors).

Special populations

Children and Adolescents

Children are persons below the age of majority according to local laws. Many children worldwide are exposed to HIV infection through perinatal transmission, breastfeeding, blood transfusion, sexual activity, sexual abuse or injection drug use. In 23 designated priority countries, 72% of new HIV infections occurred in girls aged 15-19 years (UNAIDS 2010, UNAIDS 2017). Regrettably, progress for HIV prevention among adolescents has been slow. As a public health matter, a wide range of effective prevention options is clearly needed for this critical at-risk population, which will require enrolling adolescents in HIV prevention research. However, their inclusion raises a number of important ethical, social and legal challenges (MacQueen and Karim 2007, WHO 2018). Adolescents may be especially vulnerable to research-related risks, while they have evolving autonomy to make decisions (SAT 2017).

These concerns are often reflected in local laws aiming to safeguard children and adolescents. These include laws related to the legal age of consent to research enrollment, sex, health services; requirements for emancipation; and laws for mandatory reporting of abuse or neglect. Researchers should be aware of such laws and their implications for enrolling adolescents in research.

Laws requiring parental consent for research with children or adolescents under the age of consent may deter enrollment (especially among those who do not wish their parent or guardian to be aware of their sexual behavior or sexual identity) or skew enrollment towards lower-risk children or adolescents. In such instances, alternative consent strategies that provide adequate protections for children and adolescents should be explored, and explicitly reviewed by IRBs/RECs. Consent strategies implemented by study staff and consent materials developed for children or adolescent participants should be tailored to their age and developmental stage.

It is advisable to ensure appropriate engagement of adolescent representatives, including involving them on existing advisory structures such as CABs/CAGs or developing separate youth advisory boards to provide input on key study aspects such as recruitment and consent.

Pregnancy and Lactation

In biomedical HIV prevention trials pregnancy and lactation present concerns about the well-being of fetuses and breastfeeding children, respectively. Regulatory agencies and sponsors generally require participants who become pregnant during trials of products whose safety and efficacy have not yet been established discontinue it, but continue to be followed if they are willing so as to be able to provide some initial data on safety of product use during early pregnancy. However, stopping the use of a study product by people who become pregnant has many drawbacks, including potential bias of study findings, negative impacts on statistical power, and loss of important safety and efficacy data on HIV prevention interventions for pregnant persons and their fetuses (Lyerly 2019).

CIOMS states that when there is no evidence of a potential harm to the fetus, participants who become pregnant should not be automatically removed from the study, but offered the option to continue or end their participation. However, there are a number of ethical and regulatory issues to consider when deliberating about continuing the use of a study product in persons who have become pregnant during an HIV prevention trial. Researchers, sponsors, and ethics committees should assess whether there are circumstances in which people who become pregnant can continue to receive the study product considering relevant research regulations, CIOMS (2016) guidelines 18 and 19, and the best available knowledge of the benefits and risks. Assessing this sensitive issue requires community engagement. Should it be potentially acceptable to continue the use of a study product during pregnancy, the risks and benefits of continued study participation must be clearly conveyed to pregnant participants during a re-consent process.

In areas of high fertility and substantial HIV prevalence, those who are or become pregnant might use an approved preventive intervention, even if it has not been proven safe for them during pregnancy or their fetuses. Therefore, safe inclusion of pregnant participants in HIV prevention research should be a scientific and ethical priority (Lyerly et al. 2008).

Nevertheless, research with pregnant persons should only be initiated after careful consideration of the best available relevant data (CIOMS 2016). Current regulations and guidelines focus specifically on cisgender women, but consideration should also be given to transgender men. US federal regulations state that where scientifically appropriate the study product must have been proven safe in preclinical trials with non-human animals and non-pregnant women, and the risk to the fetus should be minimal unless the research holds out the prospect of a direct benefit to the women or the fetus (cf. 45 CFR 46.204). Researchers, sponsors, and ethics committees should evaluate the strength of current evidence pertaining to the potential beneficial and harmful effects to both pregnant persons and fetuses on a product-by-product basis.

Assessing Emerging Data about Potential Fetal Risks

During the conduct of an HPTN trial that was evaluating the preventive efficacy of a long-acting injectable, cabotegravir (CAB) in women of reproductive age in sub-Saharan Africa, data emerged concerning the possible teratogenicity of a related medication dolutegravir (DTG). HPTN and the trial sponsor contemplated three options: (1) continuing the study; (2) pausing the study; and (3) closing the study. Unlike the participants who were not infected with HIV upon trial enrollment, the DTG data were obtained from an observational study of women living with HIV. While more information about these findings was being sought, enrollment in the trial was paused. After careful consideration of the data, the teratogenic risk in the HIV prevention trial was thought to be low, so a decision was made to resume the trial, following re-consent of participants and the inclusion of long-acting reversible contraception (LARC) to reduce the likelihood of fetal exposure. During the re-consent process participants were informed about the emerging findings and the need for them to remain on LARC during and after CAB injections for at least a year was reinforced.

If the potential of harming the fetus due to product use is uncertain, researchers face a serious predicament when working in settings where access to abortion is constrained legally or through institutional policy. According to CIOMS, such research should be only be conducted in settings where women can be guaranteed access to a safe, timely and legal abortion in the event that participation in the research renders the pregnancy unwanted (CIOMS 2016). Nonetheless, given widespread laws where HIV is highly prevalent, this requirement could preclude important HIV prevention efforts.

Responsibilities towards bystanders

In some HIV prevention research, non-participants may be exposed to research-related risks, raising questions about potential responsibilities to them (Bärnighausen 2019, Eyal et al. 2019, Eyal and Wikler 2019). For example, men may be exposed to physical risks from an experimental vaginal gel when their sexual partners are enrolled in microbicide research. Despite the dearth of clear guidance regarding bystanders (Eyal and Wikler 2019), explicit consideration should be given to the potential risks for bystanders affected by the research and minimize foreseeable risks to them. In addition, it may be ethically appropriate to develop means to inform them and perhaps obtain their explicit consent if the risks are substantive (Shah et al. 2018). Relevant considerations include feasibility and potential harms to enrolled participants, such as adverse actions towards them by their sexual or domestic partners. Primary consideration should be given to the autonomy, welfare and safety of participants, but significant, reasonably predictable injuries to non-participants must also be considered and avoided. Community engagement and IRB/REC review should facilitate deliberation about these issues. Finally, the approach being implemented should be made clear to participants during the consent process.

GUIDANCE POINT 6. CONSENT, ASSENT, PERMISSION AND RE-CONSENT

Each site involved in HIV prevention research should develop, implement and document and implement appropriate informed consent, assent, permission and re-consent processes tailored to the needs of participants.

- ***Status:*** Ethical obligation
- ***Responsible and accountable:*** Researchers and sponsors

Consent

HIV prevention researchers must be committed to developing and using rigorous informed consent processes for this research. Informed consent has a number of distinct requirements. The prospective participant:

- must be provided with sufficient understandable information about the proposed research, alternatives to participation and the opportunity to have their questions answered;
- must have adequate capacity to engage in decision-making about research participation; and
- must express agreement explicitly in some way, by signing or making a personal mark on a form, or by oral consent.

From an ethical perspective, informed consent is valid only if all of these substantive requirements are met. Since there may be challenges in meeting these requirements in some settings, it is important to design communication methods that are effective and culturally appropriate in content, format and delivery. Where applicable and feasible, formative research should be used to develop a customized consent process (possibly using alternative media such as pictures, flip charts or video) for a specific study. Along these lines, researchers should attempt to utilize evidence-based strategies for developing and implementing concise informed consent forms (Corneli et al. 2017, Corneli and Sugarman 2017).

The study team should also develop mechanisms to evaluate potential participants' comprehension of the study. A variety of strategies may be suitable for this purpose, including discussion during the informed consent process, use of informed consent comprehension checklists or quizzes, or interviews with potential participants. In high risk or especially complex research, it may be ethically appropriate to require participants to formally demonstrate comprehension using a standardized quiz.

Researchers must respond appropriately to potential gaps or limitations in the general literacy, health literacy or research literacy of research populations. Provisions to gain consent orally (with the potential involvement of a witness) should be in place to accommodate non- or semi-literate participants. In some settings, it may be necessary to hold pre-research discussions about general health and HIV/AIDS issues. Preparatory research literacy efforts may also be needed to improve community understanding of culturally unfamiliar scientific concepts or study procedures. As study designs evolve and become more complex, research literacy concerns will need to be revisited even among communities with previous HIV prevention research experience (see Guidance Point 5).

Communicating about research components

Studies indicate that some research participants believe erroneously that procedures or interventions conducted for research purposes (to develop generalizable knowledge) are being implemented for their personal health-related benefit. This phenomenon (typically termed the "therapeutic misconception" in trials involving therapies and the "preventive misconception" for trials involving prevention modalities) may reflect inadequate consent and underscores the importance of clearly communicating the purpose of various research components. To facilitate this communication, study site preparations for the implementation of specific research protocols need to ensure that these distinctions are made clear. As a practical matter, this could include the construction of a table summarizing components of research:

- provided as part of the scientific objectives of the study, or needed to conduct the study safely and successfully; and
- provided for non-scientific reasons, primarily to help address participants' needs and to benefit the research participant.

Such a table might also stipulate whether and for how long access to each component will be provided after the end of research participation (see also Guidance Point 10).

This table could 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 during the informed consent process. The research team could also consider presenting this table (after it has received regulatory approval) during the informed consent process for new participants and at follow-up visits for participants already enrolled (Corneli et al. 2006, Corneli et al. 2017).

Avoiding undue inducement

Most research involves some type of inducement, that is, ways of motivating prospective research participants to join a study. HIV prevention studies commonly include potential inducements such as monetary payments for participation as well as access to care services and prevention modalities.

Monetary payment for participation can take various forms. For example, reimbursing participants for expenses they incur due to the study, such as travel costs for study visits. Payment can also be provided for the time related to participation (Gelinas et al. 2018). In addition, payments may serve as incentives for participants to adhere to study procedures and return for study visits.

Researchers should avoid undue inducements, which are those incentives that are so attractive that they can cause research participants to join a study against their own best judgment and interests. What makes an inducement 'undue' depends on a number of contextual factors, including the size of the offer, the potential risks involved in the study, and the value an inducement may have in a particular context (Mngadi et al. 2017). To offer a substantial monetary inducement to an impoverished research participant to join a highly risky study may be exploitive and a violation of the ethical principle of respect for persons.

Accordingly, any proposed payment schedules and amounts should be discussed with community stakeholders and approved by the IRB/REC. Community consultation can be helpful in determining appropriate payment, given that a seemingly modest monetary inducement may be highly valuable in resource-poor settings. Researchers should inquire about inducements provided in past similar studies, and any perceived concerns with those inducements.

Nevertheless, concerns about possible undue inducement should not be used to rationalize inappropriately modest inducements, thereby limiting remunerations to research participants. Any potential inducements, their justification, and the process of establishing their appropriateness should be carefully considered and clearly specified in the study protocol.

Waivers of written documentation consent

While it is preferable that the informed consent of the participant be recorded in some way (by signature or mark), circumstances may arise where respect for persons is better served by waiving this requirement and obtaining oral consent instead. For example, the revised Common Rule states that participants may be "members of a distinct cultural group or community in which signing forms is not the norm" (45 CFR 46.117.c.1.iii). In some settings, there may be deep cultural distrust about signing official documents. In some studies, a signature may be the only identifier linking the study with the participant and waiving written documentation of consent may enhance confidentiality protections. Exceptions to written informed consent must take into account the potential risks of the study and ensure that the exception will not adversely affect the welfare and rights of research participants. Community consultation regarding the appropriateness of written documentation and its alternatives may be helpful in certain settings. However, there may be some regulatory limitations to such waivers that must be considered by IRBs/RECs, sponsors and regulators.

Waivers of consent

While obtaining informed consent is an ethical obligation for research involving human participants, in some cases it may be ethically justifiable not to seek and obtain consent at all. For example, observational studies and some other types of 'not greater than minimal risk' studies may not require consent of participants under US government regulations (45 CFR 46.117.c.1.iii) and may be compatible with fundamental ethical principles. Discussions about waiving consent entirely should be initiated among key stakeholders (particularly researchers, community representatives, and ethics review boards) early in the research design process (CIOMS guideline 10)(CIOMS 2016).

Parental or guardian permission

The permission of parents or legal guardians is typically required for the enrollment of children in research. However, in some jurisdictions, waivers of parental permission may be permitted if the responsible IRB/REC determines that the criteria for doing so under relevant local policies have been met, for example, that the research poses minimal risk. Across the globe, both adolescent males who have sex with males and adolescent transgender females have been found to be particularly vulnerable to HIV. These young people, especially those who have not disclosed their sexual and gender status to their parents, are also vulnerable to stigma and punishment from family members if they participate in HIV research. In order not to deprive this population of evidence-based HIV prevention and treatment interventions, appropriate procedures for waiving guardian permission must be considered (Fisher et al. 2017).

In general, in close collaboration with host-country experts, researchers should conduct a thorough survey of local laws related to research with children and adolescents and consent for enrollment in it (WHO 2018). When parental waivers of permission are being considered, researchers should seek ways to protect children, in close consultation with community representatives, regulatory authorities, IRBs/RECs, and local or national organizations devoted to the protection of the rights and welfare of children. The process of appointing advocates for the participation of children in such circumstances should be consistent with relevant policies and regulations (e.g., 45 CFR 46.408). Some jurisdictions have provisions for emancipated minors (e.g., children who are married) that allows them to make a variety of decisions independent of their parents, including consent for research.

Assent

In United States federal research regulations, assent is defined as “a child's affirmative agreement to participate in research” (45 CFR 46.402[b]). However, in some countries, the requirement of obtaining assent is neither part of national law nor medical practice. Regardless, the host and sponsor IRBs/RECs must determine whether children who will be recruited for a study are capable of giving assent, and if so, whether the study includes appropriate provisions for obtaining it. Where children are deemed incapable of giving assent, or where children stand to gain a benefit that is important to the health or well-being of the children and is available only within the context of research, IRBs/RECs may waive the assent requirement, if governing regulations permit them to do so.

Formative research and community consultation should explore context-sensitive approaches to gaining assent from children in research (WHO 2018). Assent should be obtained from children according to their psychological and intellectual development, rather than at any fixed age. In studies where children are HIV-positive but do not know their sero-status, conflicts arise between the requirement of assent and the disclosure of HIV status. In such cases, even if fully informed assent may not be appropriate, a gradual process of preparation for disclosure of HIV status involving parents/caregivers should be initiated in order to benefit the health of the child and protect others (Vaz et al. 2008).

Re-consent

Some HIV prevention research is conducted over a long period of time. Consequently, there can be changes to the research or in the circumstances of the participants that may require informing participants or obtaining re-consent from them. Such changes in the research may include design modifications, new information about potential risks and benefits, and additional requirements for continued participation in research. Changes in the circumstances of participants include, for example, adolescents who have gained the age of majority and women who become pregnant during a study.

General criteria for determining the need for re-consent of research participants have been proposed. Wendler and Rackoff distinguish between (a) significant changes and (b) non-significant changes; significant changes require a full re-consent procedure whereas non-significant changes necessitate using mechanisms to inform participants of modifications, but fall short of full re-consent (Wendler and Rackoff 2002). For example, a slight increase in volume of a blood draw should not be considered sufficient grounds for re-consent since this would not significantly impact the welfare or rights of participants. In such cases, researchers might describe the changes and seek participants’ oral agreement to proceed, documenting this process in participants’ study files. Such an approach should be reviewed and approved by the research ethics committees overseeing the research.

Particularly (but not exclusively) in longitudinal studies, research participants' understanding of the research may change over time. This may be due to the complexity of the study, uncorrected initial misunderstandings about the nature of research, or rumors circulating in the local community. In studies where misunderstandings are foreseeable or arise, researchers should periodically assess comprehension, correct misunderstandings, and respond to rumors in the community. Similarly, if verbal or non-verbal indications of dissent or discomfort with participation are present, study staff should seek to identify and address concerns and remind the participants that their involvement in the research is voluntary and that they are free to withdraw.

Use of biospecimens

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

- Whether it is possible to participate in the research without having biospecimens collected
- Who will have access and control over the biospecimens
- Where the biospecimens will be analyzed and stored
- How the biospecimens in the current study will be used
- What possible additional uses will be made of the biospecimens (e.g., future studies, commercial use) and whether participants will be re-consented or be able to opt-out of such future uses
- Whether the possible benefits of research on biospecimens are likely to be shared with participants or local communities
- Whether participants will be informed of health conditions or health-relevant information (e.g., genetic vulnerabilities) that might be noted in analyses of biospecimens
- Whether participants' identifying information or links to their identifying information (i.e., codes) will be maintained with the biospecimens

While the revised Common Rule states that "broad consent for the storage, maintenance, and secondary research uses of identifiable private information or identifiable biospecimens…is permitted as an alternative to the [usual] informed consent requirements", additional provisions apply if this approach is used (45 CFR 46.116.d). Regardless, local communities may be reluctant to permit the collection, storage and analysis of human tissue, partly due to rumors about what is done with biospecimens when they are exported and analyzed in a distant locale or foreign country. As such, broad consent may be more or less appropriate in some settings compared to others. In settings where broad consent is deemed appropriate, researchers should implement

best practices for obtaining it (Sugarman 2017, Cheah et al. 2018). Whenever participants opt out of future uses of their biospecimens, research teams should honor such requests by retrieving and destroying these biospecimens and document these actions.

GUIDANCE POINT 7. ADDRESSING VULNERABILITIES

HIV prevention researchers should assess, monitor and respond to the social, cultural and other factors that may place research participants at heightened risk.

- ***Status:*** Ethical obligation
- ***Responsible and accountable:*** Study team and researchers

Rather than labeling whole groups of individuals as vulnerable, vulnerability is better characterized in terms of specific factors or conditions that place the health and well-being of individuals at heightened risk in their daily lives. That is, there are specific factors that can render individuals vulnerable (Luna 2009, CIOMS 2016), including: age or level of maturity; criminalization; discrimination; gender inequality; sexual orientation and gender identity; immigration status; inadequate local health services; level of education, reproductive health education or education about HIV/AIDS; political instability; political oppression; poverty; and stigmatization. Further, some of these factors may compound one another (Luna 2019).

HIV prevention researchers should identify and evaluate the key vulnerability factors prevalent in the community where research is being planned. It is beyond the scope of most research to wholly rectify these factors, but researchers should avoid exploiting or exacerbating existing factors for vulnerability and try to minimize them when feasible and appropriate (Luna 2019). For example, researchers may opt to conduct recruitment activities and study visits away from high visibility areas, such as clinics or hospitals, to mitigate potential stigmatization of participants. They may also undertake awareness-raising in the local community to reduce HIV stigma. Some particularly relevant factors associated with vulnerability in HIV prevention research are poverty, social inequality, stigmatization and discrimination; each of these is described below in some detail.

Poverty

Poverty may increase the vulnerability of participants in HIV prevention research. For example, some participants (e.g., those who engage in sex work) may forgo elements of the standard of prevention package, such as using condoms, to ensure greater income while placing themselves at

higher risk of becoming infected. Other participants may risk serious medication side-effects partly due to inadequate nutrition as a consequence of poverty. Economically disadvantaged participants are also likely to have ancillary care needs (See Guidance Point 10).

Social inequality

Being part of a group that has a low status in some societies — such as people who use drugs (PWUD), MSM, transgender people, sex workers, homeless individuals, illiterate persons, migrants or undocumented immigrants — can significantly affect whether and how an individual participates in HIV prevention research. Low social status may make certain groups hard to reach and this can pose significant challenges to recruitment and retention. Low social status may make potential participants reluctant to join HIV prevention research.

Given the high prevalence of gender inequality worldwide, and the feminization of the HIV epidemic globally, inclusion of female participants in HIV prevention research is both necessary and ethically challenging. Women may face practical obstacles to participation in research, given that they are often disproportionately burdened with caring for children, the sick or the elderly. Recruitment of women into research studies where they are required to use contraception may be difficult when a high cultural value is placed on fertility and childbearing. Female participants may be potentially vulnerable to social harms, such as being accused of infidelity by their partners, and subject to partner or family abuse.

Accordingly, research teams should take special care to address the potential social inequality of female participants, for example, during study-related contacts at their homes or when providing study-related information to them, and making provisions for childcare support and transportation, when appropriate.

Stigmatization

Some individuals (such as PWUD, MSM, transgender persons, and sex workers) engage in behaviors that may be regarded by others as violations of moral, religious or legal norms, and which therefore are the object of strong disapproval or active punishment and harm by many sectors of society. Such individuals may be subject to police abuse, community humiliation, neglect by health care workers, or prejudice from social service or government agencies. They may also face stigma and abuse within their own families. Consequently, recruitment of such individuals in HIV prevention research may result in an increased potential for social harms if they are thereby identified as ‘at risk for HIV’.

When recruiting from known stigmatized groups, researchers should integrate approaches to stigma-reduction into their research. This might include: information gathering with formative

research to identify forms of stigma prevalent in the community (such as rejection and physical exclusion of individuals from family homes, or common denigrating labels placed on persons living with HIV/AIDS); raising stigma awareness among those involved in research implementation such as research staff, local clinicians, nurses and field workers; being mindful of language (especially in local translation) used to describe the study and study population in recruitment documents, consent forms and fact sheets; having community engagement activities partly devoted to stigma reduction; ensuring that the research environment constitutes a private and confidential 'safe space' where participants can share their personal experiences and concerns; and collection and analysis of social harms data.

Challenges to protecting vulnerable populations in research

In many settings, PWID are stigmatized to such an extent that it can be difficult to protect PWID who enroll in HIV prevention research. PWID are often regarded by local governments, local police authorities and many community members as criminals, and research involving them may be discouraged. When research does occur, governments may monitor those enrolled; local police may have the names of all participants and observe them coming in and out of the clinic. In such a political and social context, standard confidentiality protections for these research participants is insufficient, so researchers need to identify additional risk-reduction approaches for this population. This can involve educating police about proposed research in order to minimize risk to participants and developing and implementing other risk mitigation plans (Sugarman et al. 2014, Sugarman et al. 2018). In contrast, if it is not possible to minimize risks, it may not be appropriate to conduct the research at that site.

Discrimination

In some settings, people living with HIV may enjoy the same rights, protections and social benefits as those who are not infected; however, in other settings they may face obstacles gaining or retaining employment, medical care or legal representation. When a person participates in HIV-prevention research, they may be wrongly considered to be living with HIV and for that reason may face discrimination.

Researchers should explore ways to minimize potential discrimination due to participation in HIV prevention research by joining efforts and sharing information with local human rights groups and civil society organizations that are dedicated to protecting people living with HIV as well as consulting such groups and and organizations about protections for participants, and incorporating these into the research protocol, site preparation, and SOPs as appropriate (See Guidance Point 3).

GUIDANCE POINT 8. ETHICAL REVIEW OF RESEARCH

Independent ethics review committees in host countries should review HIV prevention research.

- ***Status:*** Ethical obligation
- ***Responsible and accountable:*** Sponsor, researchers, research sites, and ethics review committees

International ethics guidance documents agree on the need for independent ethics review of research but differ on whether research protocols must be submitted for ethical review in the localities where the research will be conducted. The current Declaration of Helsinki (World Medical Association 2013) and the CIOMS guidelines (CIOMS 2016) state that research protocols should be reviewed by an independent ethical body, but do not specify whether this review should be local. In contrast, the UNAIDS *Ethical considerations in biomedical HIV prevention trials* (UNAIDS/WHO 2012) states that it is unethical to conduct HIV prevention research if there is not adequate local review, even if the protocol has been reviewed and approved elsewhere.

Despite the lack of specific requirements in some ethics guidance documents, the nature of much HIV prevention research argues for the need for approval of a local ethics review body. Local IRBs/RECs can have a better appreciation of the study context, potential vulnerabilities of community stakeholders and participants, and study-related risks and benefits given local cultural norms and social realities.

All IRBs/RECs should at minimum be independent, have professional and gender diversity of members, and include non-institutional members. Where a local IRB/REC or similar ethics review body exists but has limited capacity, initiatives should be taken to strengthen ethics review capacity before research begins. This could include ensuring the committee has access to relevant training or materials, such as resource documents regarding HIV prevention research. Given the possible conflicts of interest when researchers who conduct the studies help to strengthen the committee that reviews their studies, it might be prudent to engage others in such capacity-strengthening efforts. Regardless, these efforts should be designed and conducted as collaborative initiatives in partnership with the local IRB/REC.

However, in some cases, such as multi-site studies among similar populations, it may be advantageous not to have ethics review at each site in order to avoid duplicative procedures, excessive bureaucratic burdens, and unhelpful variations among IRBs/RECs determinations in

different sites that result not from differences in local contexts but rather from idiosyncratic factors. Of note, the revised US Common Rule states that "any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB [sIRB] for that portion of the research that is conducted in the United States" (45 CFR 46.114.b.1). The NIH has also issued guidelines mandating use of sIRBs for multisite studies it funds. In such instances, strong efforts should be made to ensure that the sIRB obtains and considers, in its review, appropriate knowledge of local contexts.

GUIDANCE POINT 9. STANDARD OF PREVENTION

HIV prevention researchers should partner with key stakeholders to provide a package of effective, comprehensive and sustainable prevention services to all participants in HIV prevention research.

- ***Status:*** Ethical obligation (provision of prevention package) and ethical aspiration (content of prevention package)
- ***Responsible and accountable:*** Study team and sponsors

Standard of prevention refers to the aggregate services and interventions available to help reduce the risk of HIV infection. The principle of beneficence obligates researchers and sponsors to minimize risks to participants in HIV prevention trials, which means that participants should have access to effective means to minimize their risk of acquiring HIV during the course of the research. These means considered collectively are sometimes referred to as the "prevention package".

It can be practically and ethically challenging to determine the content of the prevention package. Some guidance indicates that the prevention package should include appropriate counseling and all 'state of the art' HIV risk reduction methods (UNAIDS/WHO 2012), however, this may be infeasible in practice. For example, in some communities, male circumcision may be considered inappropriate to include in a prevention package due to strong religious and cultural objections. In some countries, it may be illegal to provide certain prevention methods such as needle exchange. Further, requiring all 'state of the art' prevention methods to be provided to participants is arguably anachronistic given that there are now many known, effective means of preventing HIV infection; and any one individual may not need all such methods to prevent infection. In addition, there are some broader considerations associated with offering an extensive array of HIV prevention methods to participants. First, when these methods are not generally available to non-participants in the community, there may concerns about the potential for undue inducement to participate. Second, a very robust prevention package could potentially compromise the ability of

a study to detect effects of the experimental modality, which undermines the scientific validity and social value of the research.

Researchers should adopt an approach to the standard of prevention that is pragmatic and context-sensitive, but also aspirational. An aspirational but pragmatic approach is underpinned by the ethical principles of beneficence and justice. The necessary conditions for a modality to be included in the prevention package is that it is 1) known to be an **effective means of prevention** for HIV transmission; 2) **practically achievable** as a standard in the local setting; and 3) **reasonably accessible** to those at risk of HIV infection who desire to use it. Although these conditions are necessary in determining the standard of prevention, they are not sufficient to warrant inclusion. The standard of prevention offered to participants should not be so radically superior to that available to non-participants in the surrounding community such that it could not be feasibly integrated into local services. At the same time, the standard of prevention should not replicate sub-standard prevention services in the community. If the standard of prevention for a study is predicated on the lack of local resources or problematic policies/legislation, researchers must carefully consider whether the research inappropriately reinforces an inadequate and modifiable status

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

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 research. This does not preclude the possibility of improving on the existing local standard of care, but it does require such improvements are on a par with the requirements of a particular study, for example laboratory procedures needed for the confirmation of outcome measures. Additionally, such services should not undermine other existing services in the community, for example, by requiring that limited resources be shifted to provide the new services.

Reasonably accessible indicates that the services are free or at a cost within the means of research participants and that they can be implemented safely and legally within the research participants' community. While it is preferable to offer all aspects of the preventive services at the research site, it is generally acceptable for some of these services to be provided through referral to an entity that meets these criteria for accessibility, if direct provision of the services would critically overwhelm the capacity of the research staff, or if the service requires expertise or specialized skills that go beyond what is reasonably necessary for implementation of the research.

quo, which may need to be balanced with the potential of the research to convincingly demonstrate the superior impact of a preventive approach in comparison to current community standards of prevention.

Every HIV prevention research protocol should explicitly consider – as a minimum package – ensuring access to HIV voluntary counseling and testing, HIV and STI risk reduction counseling, male and female condoms, and established biomedical prevention methods (e.g., oral PrEP) to participants. In research involving PWID, risk reduction counseling related to substance use and access to sterile needles and syringes must also be considered. When determining components of the prevention package, it is essential to ensure that it comports with local policies and regulations (e.g., is a medication used for PrEP registered for use within the jurisdiction). Regardless, when these basic preventive options are not included in the prevention package or in a comparator arm of a trial, the reasons for not doing so should be explicitly justified. On the other hand, beyond these basic options, each site and study team may identify additional services to be provided.

Of course, there is a continuum of how components of the prevention package services may be implemented among different countries, regions, or clinics in the same research protocol. For example, researchers should consider whether they should:

- provide information about the known effectiveness of the method
- actively promote it as part of the counseling process
- provide referral mechanisms to services in the local health care system, or
- provide the service directly to participants.

Researchers should consult with community stakeholders and relevant stakeholders more broadly, to address the issue of standard of

Use of PrEP in Prevention Clinical Trials

Following the approval of FTC/TDF PrEP, the HPTN has fielded the Antibody Mediated Prevention (AMP) trials [NCT02716675; NCT02568215] that are evaluating the feasibility, safety and efficacy of passive immunization with the monoclonal antibody VRC01 in trials that include a placebo control arm. These phase 2b trials are not intended to lead to licensure, but rather to 1) inform the field of vaccine research and 2) establish whether monoclonal antibodies are a promising concept for future monoclonal antibodies products (e.g., dual use, longer acting, or more potent). One trial involves MSM in the Americas and the other women in Sub-Saharan Africa. In these multisite trials, any participant was permitted to use FTC/TDF PrEP, though it was projected that such use would be low in some sites and unavailable in others. Enrollment in the trial was rapid and retention was excellent. PrEP use ranged from 0% at some sites to 50% at others. PrEP availability adds complexity to the interpretation of trial results, though it was not expected to adversely affect the overall findings.

prevention. Researchers should identify what prevention services are available to the local community and whether (and to what extent) the prevention package offered in the research exceeds the local prevention standard of care.

The provision of prevention services in the local community may change over the course of a trial; therefore, researchers should periodically reassess local standards compared to the prevention package offered by the research.

Researchers should also serve as resources to host-country advocates seeking to modify local policies or laws that undermine the use of evidence-based prevention methods, for example, the exchange of sterile injection needles (Lancaster et al. 2018). Researchers should engage in advocacy for improved prevention programs in the community before or in tandem with investing resources in the testing of alternative methods.

GUIDANCE POINT 10. STANDARDS OF CARE AND TREATMENT

HIV prevention researchers should strive to provide care and treatment to participants that exceed local standards of medical services, yet does not impose undue influence to participate in research.

- ***Status:*** Ethical obligation (establishing standards of care and treatment) and ethical aspiration (content of standards)
- ***Responsible and accountable:*** Researchers and study team

Standards of care and treatment refer to the package of services the participant can expect to receive in terms of medical care or treatment. HIV prevention researchers must be knowledgeable of the current standards of care in the local community, provide at the very least equally adequate care services, and seek to enhance standards of care both within and outside the research study especially if local standards are low. Similar to standards of prevention, standards of care and treatment must be practically achievable.

There are different domains of care to be considered:

- Care provided for study-related reasons (“Direct Care”)
  - Care and treatment provided to participants for study-related reasons
  - Care and treatment for research-related harms

- Care provided for non-study related reasons ("Ancillary Care")
  - Care and treatment provided because of 'non-scientific' reasons to participants
  - Care and treatment for those screened for the research who fail to meet study inclusion criteria due to a medical condition (such as HIV infection)

Care and treatment provided for study-related reasons (Direct Care)

Care and treatment provided to participants for study-related reasons

Enrolled participants will necessarily have access to care that is provided for study-related reasons. In an HIV prevention study, this might include monitoring to ascertain the effects of the experimental intervention and providing access to contraception when there are concerns about preventing pregnancy due to exposure to a research intervention that may be harmful to a fetus.

The care to be provided as part of the study should be determined in consultation with relevant stakeholders. Researchers should clearly express the package of care and treatment that participants will receive for study-related reasons in the study protocol and in the consent process.

Care and treatment for research-related harms

At times, research participants might be harmed as a result of the research that requires treatment. International guidance documents (e.g., CIOMS 2016, Guideline 14), as well as some national policies, recommend or require that participants receive compensation for research-related injuries. However, some sponsors, such as the NIH are prohibited from spending funds for such purposes. Compensation for injury can sometimes be handled at the site level through arrangements with institutions conducting the research. In some cases, funds can be used to purchase insurance to cover compensation for injury, when national regulations in the host country require that this provision be in place. Regardless, researchers should identify opportunities through sponsors or otherwise to provide a mechanism for providing care and treatment to participants for research-related harms.

In particular, those who become HIV-infected in an HIV-prevention trial should receive treatment. Beyond obligations of beneficence, there are different ways to defend such a right. Some argue as a matter of reciprocal justice that participants should get treatment in return for their contributions to the research. Others argue that treatment should be provided to avoid ethical double standards in internationally collaborative research, because participants in HIV prevention trials in resource rich countries routinely have access to antiretroviral treatment. Accordingly, researchers should partner with care providers, government agencies and international agencies to strive to ensure access and linkage to high-quality treatment for participants who seroconvert during HIV prevention research trials, including ART.

Nevertheless, the consent process should describe the nature of the compensation and whether care is available for research-related harms that may occur during the conduct of the study. When compensation for injuries will not be offered, this must be stated explicitly.

Care and treatment provided for non-study reasons (Ancillary Care)

For participants

Ancillary care has been defined as care provided to participants, which is not required to make a study scientifically valid, ensure a study's safety, or compensate for research-related injuries (Richardson and Belsky 2004). Monitoring drug interactions or providing care for adverse reactions to a study drug are not ancillary care. By contrast, following-up on diagnoses found by study tests but that are unrelated to the study's aims would be ancillary care. Providing ancillary care for participants may reinforce trust between researchers and participants, but can also increase inequities in health care access between participants and non-participants in the same community. Questions about ancillary care tend to arise frequently in conduct of research in resource poor settings with weak health care infrastructures (Jacobson et al. 2016). However, such questions also arise in resource rich settings where there may be inadequate services for certain conditions. For example, in HIV prevention research it may not be unusual to encounter questions about treatment for hepatitis C virus infection or for hormonal treatments for transgender persons.

The four "Ps" of ancillary care obligations for researchers are: positive duty, planning, partnership, and pragmatic steps (Participants in the Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries 2008). Positive duty reflects the moral obligation to provide some ancillary care to study participants. Planning includes having developed plans, both in general and for each protocol, for meeting the ancillary-care obligations that may be expected to arise. Partnership involves developing ancillary-care plans in dialogue and partnership with the host community, in ways that maintain respectful interaction, avoid displacing or disrupting local health care structures, and represent the population of potential study participants. Practical provisions refers to taking definite practical steps towards meeting ancillary-care obligations.

Consequently, researchers should conduct pre-research community consultation and systematic assessments to reveal the prevalent health conditions in the local population in order to anticipate at least some of the ancillary care needs of study participants. Which of these needs should be attended to if they arise during research implementation, and which should not, depends on a variety of factors (Richardson 2007) that must be adjudicated within particular contexts. However, as research is being planned, researchers should partner with key stakeholders to develop agreed-upon standards for the provision of or referral for ancillary care and take pragmatic measures to achieve them (Merritt et al. 2015).

For persons who are screened out of research

Screening procedures for HIV prevention research can identify medical conditions in prospective research participants that were previously undetected. Richardson offers a framework to evaluate the stringency of researchers' obligations to ensure access to care for persons who are being screened for research, but are not enrolled (Richardson 2007). According to this framework, the degree to which researchers are obligated to provide care depend on five factors: (1) participants' vulnerability (how badly off the person would be if they did not receive help); (2) participants' degree of dependence on the researchers (whether they lack other sources of possible help); (3) participants' uncompensated risks or burdens; (4) the depth (intensity and duration) of participants' relationship with researchers; and (5) the cost to the researchers of providing the relevant care.

Applied to the case of persons being screened for enrollment in an HIV prevention trial who are screened out because they have HIV: such persons are unlikely to have assumed major risks and burdens associated with screening procedures; researchers are unlikely to have a long or intense relationship with those being screened; and the costs of providing high quality care and treatment (particularly in high HIV prevalence settings) could be substantial. Because those who screen-out will need HIV care and treatment, and care alternatives may be inadequate, researchers must address these situations proactively through careful planning, and partnering with key stakeholders, particularly health institutions providing care, to decide upon equitable and sustainable solutions (Participants in the Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries 2008).

GUIDANCE POINT 11. INDEPENDENT DATA AND SAFETY MONITORING

HIV prevention researchers and sponsors should ensure that appropriate mechanisms for independent data and safety monitoring are in place.

- ***Status:*** Ethical obligation
- ***Responsible and accountable:*** Sponsors, researchers, and study teams

In order to help ensure the safety of research participants, the integrity of a trial, and attend to the interests of those outside the trial, there is a need for a data and safety monitoring plan for all research. These plans vary with the phase and complexity of a particular research project. For example, in a single-site early phase trial, the approach may involve a small team with the appropriate expertise to evaluate emerging incidents and data, whereas in a multicenter, Phase III randomized trial an independent Data and Safety Monitoring Board (DSMB) would likely be needed. In addition, in many trials it is commonplace to establish stopping rules at the outset of the trial that may be triggered by emerging trial data.

DSMBs (also known as Data Monitoring Committees) are advisory committees to the research sponsor that are used especially in late-stage, multi-site clinical trials that involve significant risk. The DSMB typically reviews data on safety and efficacy that may be unblinded should doing so be necessary for accurate interpretation. As such, the DSMB is able to determine whether overall harm or benefit due to the study intervention has been established or whether a clinical trial cannot achieve informative results if it continues ("futility"), and thus may recommend modifications or stopping the trial as appropriate. The DSMB is meant to operate independently of the trial's sponsors and investigators and has a number of key functions:

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

Membership on the DSMB reflects the disciplines and medical specialties necessary to interpret the data from the trials it reviews. This includes biostatisticians, clinicians who are knowledgeable about the diagnosis and treatment of the disease that is under study, community representatives and sometimes those with ethics expertise.

When a study is being overseen by a DSMB, there should be a study-specific plan that include preparations for handling information from DSMB reviews. The plan should detail how information and recommendations from the DSMB will be shared internally with research team members and externally with ethics review committees, research participants and communities, as appropriate. IRBs are responsible for monitoring ongoing research with human subjects. Consequently, responsible local IRBs/RECs should be notified of the outcome of all DSMB reviews, even if no major changes are recommended, in order to document that data and safety monitoring is occurring as expected.

DSMB Challenges Due to PrEP

The interim analysis task of the DSMB becomes particularly difficult with the use of oral PrEP among participants, as PrEP is known to reduce the incidence rate of HIV if used with high adherence. Trial characteristics (including recruitment and retention) used for planning could be very different as a result of higher or lower adherence to PrEP—information which could be known to the DSMB, but not the study team. As such, responsibility to interpret the emerging trial results and protect trial participants and the scientific integrity of the trial relies heavily on those who are charged with this monitoring function.

If early termination occurs or if there are major modifications recommended by a DSMB, these findings should also be reported in a comprehensible and timely way to local IRBs/RECs and communities hosting the research. In some cases, such as the early termination of the African male circumcision trials, the DSMB may recommend unblinding of the interim results of a study to researchers and participants when doing so is believed to be in the best interests of participants.

Special Issues for Monitoring Social Harms in HIV Prevention Studies

Given the possibility of social harms related to participation in HIV prevention trials, investigators, sponsors, IRBs/RECs and DSMBs should determine whether a particular study should include mechanisms for social harm reporting and monitoring. By explicitly asking participants about social harms at regular study visits (Sugarman et al. 2014, Sugarman et al. 2018), it may be possible to identify inadvertent harms related to participation so that measures can be taken to minimize such harms and protect participants.

GUIDANCE POINT 12. DISSEMINATING RESEARCH RESULTS

HIV prevention researchers should plan for the timely communication of HIV prevention research results to scientific audiences as well as participants, affected communities, and other stakeholders in a manner that promotes understanding and trust.

- ***Status:*** Ethical obligation
- ***Responsible and accountable:*** Study team, sponsor, researchers, and community representatives

Researchers have an ethical obligation to disseminate research results in a timely fashion not only to scientific audiences but also to participants and their communities. Participants and community stakeholders are entitled to know the results, in a timely matter, of the research their involvement made possible.

Scientific communications and data sharing

Peer-reviewed scientific communication at meetings and in journals provide a means of ensuring accuracy of scientific findings. In addition, data access plans are increasingly required as pre-requisites for study approval and publication. This has largely been driven by medical journal editors and regulatory requirements imposed by the European Medicines Agency. Access to de-identified raw data by third-party researchers is intended to promote the reproducibility of research findings and therefore benefit the scientific community and society at large (Boué et al. 2018). In addition to raw data, data sharing may include documentation about meta-data as well as tools to assist dataset accessibility. The potential ethical and scientific benefits of data sharing also include the possibility of generating new, valuable, and publicly accessible knowledge. Accordingly, researchers should incorporate plans for third-party researcher access to de-identified data into research protocols and informed consent processes.

Individual research results

In many research settings, researchers will share individual health-related research test results with participants when those results have potential health implications. However, protocols and consent forms have not always been clear about if and when such information will be provided to research participants. In light of the prevailing tension between respecting the interests and desires of participants, the responsibility of protecting participants from questionable and potentially inaccurate results, and preservation of the integrity of a trial, a report from US National Academics of Sciences, Engineering, and Medicine (NASEM) offered a set of recommendations

that leans more towards transparency with participants and away from the sometimes contradictory regulations set forth by the US Clinical Laboratory Improvement Amendments of 1988 (CLIA) and Health Insurance Portability and Accountability Act of 1996. NASEM suggests a process for returning individual results "that considers the value to the participant, the risks and feasibility of return, and the quality of the research laboratory" (p. xxvii)(NASEM 2018). Consequently, the justification for communicating individual results to participants is strengthened as the value and feasibility of returning results increases. However, in some cases it may be illegal to return research lab results that come from clinical labs that are not CLIA certified and similar regulatory conditions may be imposed by lab regulatory standards in non-US jurisdictions. Therefore, in determining whether to share individual lab results with research participants, researchers must understand applicable national and state/provincial law requirements for lab licensure and results reporting.

Regardless, researchers should have a clear plan regarding whether individual results will be communicated to participants, and if so, how and when. The plan should be documented in research protocols or other supporting documents so this approach can be reviewed by IRBs/RECs. Where possible, researchers should incorporate participants' stated needs and preferences into decision-making processes (NASEM 2018). Similar consideration should be given to deciding whether to tell participants which arm of the study they participated in and plans for how and when to do so should also be carefully documented in the research protocol (Dinnett et al. 2005).

Community communications

Both positive and negative research results should be publicly available and communicated to the community in accessible ways (Robinson et al. 2010). In addition to academic publications, potential modalities include community meetings and conferences, blogs, theater pieces, social media driven networks, community radio broadcasts, CAB newsletters, webinars, newspaper articles and television programs. The dissemination of results should be part of a comprehensive communication plan (particularly for large multi-site phase II/III trials) that conveys how a tested efficacious intervention will fit with and strengthen existing HIV prevention strategies. Communicating these results can also provide an opportunity to reinforce HIV prevention messages and combat possible rumors and concerns.

CAB/CAG input is crucial in developing an effective communication plan. Plans for dissemination of research results should be included in the study protocol or supporting documentation. Communication of research results must protect the confidentiality of individual participants, and where appropriate, communities in which the research was conducted.

GUIDANCE POINT 13. SUSTAINING CAPACITY-STRENGTHENING AND INFRASTRUCTURE

HIV prevention researchers should endeavor to ensure that the investments made in developing capacity will continue to provide benefits and opportunities for local researchers and communities after research ends.

- ***Status*:** Ethical aspiration
- ***Responsible and accountable*:** Researchers, sponsors and research sites

The capacity developed in the course of the design and implementation of HIV prevention research (see Guidance Point 3) should ideally contribute to future research activities and public health, and in that way provide a foundation for ongoing benefits to the local community once research is completed.

From the outset of a research project researchers should explore, together with local partners, individual- and organizational-level approaches for sustaining capacity (PEPFAR 2012), such as employment and training (Emanuel et al. 2004). On the individual-level, staff and research training are critical for maintaining day-to-day facility operations, as well as executing new research projects and securing funds for them. Examples of capacity sustaining activities include collaborative grant and publication-writing initiatives (including co-authorship), scientific exchanges, and technical training. Organizational-level approaches include negotiating institutional agreements for securing and designating funds for infrastructure support, developing standard operating procedures, and strategic planning. In all of these strategies, researchers should strive to cultivate a sense of ownership among key partners (Smithers 2011).

Researchers should outline approaches for sustaining capacity and infrastructure after the research in the study protocol or supporting documentation. Plans should be modified in light of updated assessments of local needs in close partnership with affected stakeholders.

GUIDANCE POINT 14. CONTINUING CARE FOR RESEARCH PARTICIPANTS

HIV prevention researchers should seek to facilitate continuity of prevention services and care for participants who still require it after research participation has ended.

- ***Status*:** Ethical aspiration
- ***Responsible and accountable:*** Researchers and study team

This guidance point concerns post-study continuation of care and treatment services, as distinguished from provision of interventions that were tested in research and found to be safe and effective (Guidance Point 15). Withdrawal of interventions that are beneficial to a person's health runs contrary to the ethical principle of beneficence.

As described in Guidance Point 10, different types of care may be included in the package of services offered to participants either for study-related or non-study-related reasons. Participants may still stand to benefit from some components of this package after research is completed. Researchers should carefully consider what post-study care will be available on the basis of factors such as the availability of the care in the community and the foreseeable health impact (on individual and public health levels) of disrupted care.

Researchers should engage other relevant stakeholders, such as community stakeholders, insurance companies, and government and/or non-government health organizations when planning for continuity of care and make evident that relevant stakeholders have been consulted about the plan. The CIOMS recommends that the plans for providing continued care should be developed through a "transparent and participatory process that involves all relevant stakeholders before the study begins" (p. 23)(CIOMS 2016). Through this process, researchers, sponsors, and other stakeholders should discuss and determine factors such as "the level, scope, and duration of any post-trial care and treatment access" (p. 23)(CIOMS 2016). Researchers and sponsors should detail their plans for proving continuity of care in the study protocol or supporting documentation so that it can be reviewed by IRBs/RECs.

When particular services that are still needed by participants will not be continued, researchers should help to ensure that there is no discontinuity of their care and treatment. After all, research studies are not a substitute for local health care systems, and therefore the burden of continued care and treatment should ultimately be borne by local health services. At a minimum, researchers should ensure active referrals for participants to local services that provide an acceptable level of care.

Where this is not available, researchers should work together with local health authorities to try to build local capacity (see Guidance Points 3 and 4). Researchers should establish meaningful partnerships with local institutions as a crucial part of developing standards of care during the research itself and to facilitate continued access to care after research is over. The *Partnering for Care* project has identified seven steps in developing systems of care related to HIV research (MacQueen and May 2008):

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

In addition, efforts should be made to develop a follow-up and monitoring system to ensure that the referral system ensures adequate health services for former participants. These efforts should explicitly address challenges in identifying continuity of care for stigmatized groups such as MSM, transgender people, sex workers, and PWUD.

Continuity of care and evolving standards of care

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

Consistent with the ethical principle of respect for persons, researchers should accurately convey the true likelihood of continuity of care to participants. Researchers should provide information about continuing care to participants in writing or through various media, such as study websites or bulletin boards.

GUIDANCE POINT 15. POST-TRIAL ACCESS TO EFFECTIVE INTERVENTIONS

HIV prevention researchers seeking to establish the efficacy of an intervention must have at minimum a preliminary plan regarding post-trial access to interventions proven to be safe and effective, which offer meaningful benefit for research participants and their communities.

- ***Status:*** Ethical obligation (preliminary plan regarding the provision of successful interventions to participants) and ethical aspiration (provision of successful interventions to participants, communities and at-risk populations)
- ***Responsible and accountable*:** Sponsor, researchers, study team and local partners

The Declaration of Helsinki (World Medical Association 2013) states that participants should be able to continue to receive interventions identified as beneficial should they continue to need it at the conclusion of the study. The position stems from ethical considerations of beneficence and justice, that is, those who carry the burdens of research should also enjoy its benefits. Furthermore, participants may want to continue using the product after the research is over.

However, there are many considerations relevant to post-study access to interventions proven to be safe and effective in a trial. Research may involve different types of interventions and immediate provision of them may not always be feasible (Haire and Jordens 2015). Male circumcision was immediately offered to participants in the non-intervention arm of a study after the protective benefit of the intervention was established (Auvert et al. 2005, Bailey et al. 2007, Gray et al. 2007). However, drug interventions may require regulatory approval and production scale up before they can be provided (Sugarman et al. 2014, Singh 2017). Moreover, in many studies, the benefits may not be of great clinical significance. For these and other practical considerations, obligating researchers to provide access to all beneficial interventions at the conclusion of research may not be reasonable.

Notwithstanding these limitations, the study team should anticipate issues of continued access to proven interventions, especially in late-stage study protocols. Researchers should create an explicit preliminary post-study access plan. While it may be unreasonable to expect a conclusive definition of these arrangements before an intervention has been tested, this plan should nevertheless be developed in early planning stages and refined as research evolves.

Researchers should address the following questions in post-study access plans:

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

- **To whom access will be provided: study participants, the communities from which participants were drawn, or others?** The wider the access, the larger the financial implications; the narrower the access, the greater risk of inequity between participants and non-participants. Researchers should engage local health institutions to incorporate the intervention into routine practice which may ease the tensions between cost and equity. Researchers should, in partnership with local and global institutions, advocate for widest practicable access to interventions beneficial to local communities and populations at risk for HIV.

- **How long access will be provided?** Provision of free, life-long access to interventions to research participants, if applicable, raises issues cost and feasibility. It may not be appropriate in some cases, for example, if long-term efficacy is unproven or long-term side effects are unknown.

Researchers should explore creative solutions to try to address regulatory obstacles to access of new and efficacious prevention approaches, such as providing participants in the control arm access to the study product (and continued access to those in the active arm), and changing the study into a long-term safety trial. Regardless, researchers should convey relevant information about post-trial access (PTA) to prospective participants during the consent process and it with them at appropriate points in the trial.

Based on the experiences of a variety of HPTN and other stakeholders involved with planning and implementing plans for PTA, a team of researchers developed recommendations for PTA (Paul et al. 2018).

Lower resource commitment

Approach PTA as a process that begins during trial design and develops as a trial progresses. Before a trial begins, consider how PTA would be provided if the intervention is shown to be safe and effective and make an initial PTA plan. Update the initial PTA plan as the trial progresses and after any significant changes in the regulatory environment, evidence of safety or effectiveness, or health-policy that may affect participants' access to the healthcare system.

Be transparent about uncertainties. Exercise particular care in defining commitments of PTA when post-trial availability of intervention depends upon factors outside of HPTN control, such as regulatory approval and/or structural barriers that participants may face in trying to access the healthcare system through which PTA would be available.

Build time into the course of study to discuss PTA with participants and prepare them to transition to healthcare system, if needed. Possible mechanisms include:

- Building in reminders about the end of the trial and options for PTA into the protocol of study visit(s). Consider including PTA discussions into a protocol checklist to ensure it happens.
- Designate a transition phase as part of the trial, e.g. an additional study visit or visits to prepare participants to transition to healthcare setting.

Higher resource commitment

Provide funding for PTA preparation activities. Actions taken during the course of trial may facilitate participant transition to regular care for post-trial access of approved, effective intervention, but they require dedicated funding. Candidate activities that could occur during the course of the trial include:

- Supporting staff dedicated to preparing participants to transition;
- Negotiating funding from manufacturer or sponsor for limited "bridge supply" of drugs to cover delays participants may experience during transition to PTA; and
- If funding mechanism allows, providing transportation support (e.g., metro cards) that participants could use beyond length of trial.

Invest in post-trial follow-up with participants to evaluate whether PTA plans were effective in enabling participant to continue access as desired.

CONCLUDING NOTE

This ethics guidance document expresses the fundamental ethical principles to which HIV prevention researchers should subscribe and specifies the ethical obligations and aspirations of researchers and other stakeholders in regard to the conduct of HIV prevention research. This document will likely be revisited and revised in response to new developments in HIV prevention research, revised policies, and evolving ethical debates.

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REFERENCES

amfAR. 2015. Best Practices Guidance in Conducting HIV Research with *Gay, Bisexual, and Other Men Who Have Sex with Men (Msm) in Rights-Constrained Environments*. New York: IAVI. Available at: https://www.avac.org/sites/default/files/resource-files/RespectProtectFulfill2015.pdf.

Arreola, S., G.-M. Santos, J. Beck, M. Sundararaj, P. A. Wilson, P. Hebert, K. Makofane, T. D. Do, and G. Ayala. 2015. "Sexual Stigma, Criminalization, Investment, and Access to HIV Services among Men Who Have Sex with Men Worldwide." *AIDS and Behavior* 19(2): 227–234.

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

Baeten, J. M., D. Donnell, P. Ndase, N. R. Mugo, J. D. Campbell, J. Wangisi, J. W. Tappero, E. A. Bukusi, C. R. Cohen, and E. Katabira. 2012. "Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women." *New England Journal of Medicine* 367(5): 399–410.

Bailey, R. C., S. Moses, C. B. Parker, K. Agot, I. Maclean, J. N. Krieger, C. F. Williams, R. T. Campbell, and J. O. Ndinya-Achola. 2007. "Male Circumcision for HIV Prevention in Young Men in Kisumu, Kenya: A Randomised Controlled Trial." *The Lancet* 369(9562): 643–656.

Bärnighausen, T. 2019. "Sex Partners as Bystanders in HIV Prevention Trials: Two Test Cases for Research Ethics." *Clinical Trials* 16(5): 455–457.

Baron, D., T. Essien, S. Pato, M. Magongo, N. Mbandazayo, F. Scorgie, H. Rees, and S. Delany-Moretlwe. 2018. "Collateral Benefits: How the Practical Application of Good Participatory Practice Can Strengthen HIV Research in Sub-Saharan Africa." *Journal of the International AIDS Society* 21: e25175.

Boué, S., M. Byrne, A. W. Hayes, J. Hoeng, and M. C. Peitsch. 2018. "Embracing Transparency through Data Sharing." *International Journal of Toxicology* 37(6): 466–471.

Cheah, P. Y., N. Jatupornpimol, B. Hanboonkunupakarn, N. Khirikoekkong, P. Jittamala, S. Pukrittayakamee, N. P. Day, M. Parker, and S. Bull. 2018. "Challenges Arising When Seeking Broad Consent for Health Research Data Sharing: A Qualitative Study of Perspectives in Thailand." *BMC Medical Ethics* 19(1): 86.

Council for International Organizations of Medical Sciences (CIOMS). 2016. *International Ethical Guidelines for Health-Related Research Involving Humans*. Geneva: CIOMS. Available at: https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf.

Cohen, M. S., Y. Q. Chen, M. McCauley, T. Gamble, M. C. Hosseinipour, N. Kumarasamy, J. G. Hakim, J. Kumwenda, B. Grinsztejn, and J. H. Pilotto. 2016. "Antiretroviral Therapy for the Prevention of HIV-1 Transmission." *New England Journal of Medicine* 375(9): 830–839.

Coltart, C. E., A. Hoppe, M. Parker, L. Dawson, J. J. Amon, M. Simwinga, G. Geller, G. Henderson, O. Laeyendecker, and J. D. Tucker. 2018. "Ethical Considerations in Global HIV Phylogenetic Research." *The Lancet HIV* 5(11): e656–e666.

Corneli, A., E. Namey, M. P. Mueller, J. Tharaldson, S. Sortijas, T. Grey, and J. Sugarman. 2017. "Evidence-Based Strategies for Shortening Informed Consent Forms in Clinical Research." *Journal of Empirical Research on Human Research Ethics* 12(1): 14–25.

Corneli, A., B. Perry, K. McKenna, K. Agot, K. Ahmed, J. Taylor, F. Malamatsho, J. Odhiambo, J. Skhosana, and L. Van Damme. 2016. "Participants' Explanations for Nonadherence in the FEM-PrEP Clinical Trial." *Journal of Acquired Immune Deficiency Syndromes* 71(4): 452–461.

Corneli, A. and J. Sugarman. 2017. "Reducing Consent Form Length: Stakeholder Support, Evidence-Based Strategies, and Regulatory Requirements." *IRB: Ethics & Human Research* 39(2): 18–20.

Corneli, A. L., M. E. Bentley, J. R. Sorenson, G. E. Henderson, C. Van der Horst, A. Moses, J. Nkhoma, L. Tenthani, Y. Ahmed, and C. M. Heilig. 2006. "Using Formative Research to Develop a Context-Specific Approach to Informed Consent for Clinical Trials." *Journal of Empirical Research on Human Research Ethics* 1(4): 45–60.

Dinnett, E. M., M. M. Mungall, J. A. Kent, E. S. Ronald, K. E. McIntyre, E. Anderson, A. Gaw, and P. S. Group. 2005. "Unblinding of Trial Participants to Their Treatment Allocation: Lessons from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)." *Clinical Trials* 2(3): 254–259.

Doussau, A. and C. Grady. 2016. "Deciphering Assumptions about Stepped Wedge Designs: The Case of Ebola Vaccine Research." *Journal of Medical Ethics* 42(12): 797–804.

Emanuel, E. J., D. Wendler, J. Killen, and C. Grady. 2004. "What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research." *The Journal of Infectious Diseases* 189(5): 930–937.

Eshleman, S. H., S. E. Hudelson, A. D. Redd, L. Wang, R. Debes, Y. Q. Chen, C. A. Martens, S. M. Ricklefs, E. J. Selig, and S. F. Porcella. 2011. "Analysis of Genetic Linkage of HIV from Couples Enrolled in the HIV Prevention Trials Network 052 Trial." *The Journal of infectious Diseases* 204(12): 1918–1926.

Eyal, N., J. Kimmelman, L. G. Holtzman, and M. Lipsitch. 2019. "Regulating Impact on Bystanders in Clinical Trials: An Unsettled Frontier." *Clinical Trials* 16(5): 450–454.

Eyal, N. and D. Wikler. 2019. "Ethical Complexities of Responding to Bystander Risk in HIV Prevention Trials." *Clinical Trials* 16(5): 458–460.

Fay, H., S. D. Baral, G. Trapence, F. Motimedi, E. Umar, S. Iipinge, F. Dausab, A. Wirtz, and C. Beyrer. 2011. "Stigma, Health Care Access, and HIV Knowledge among Men Who Have Sex with Men in Malawi, Namibia, and Botswana." *AIDS and Behavior* 15(6): 1088–1097.

US Food and Drug Administration (FDA). 2019. *Framework for FDA's Real-World Evidence Program*, December 2018. Available at: https://www.fda.gov/media/120060/download.

Fisher, C. B., A. L. Fried, M. Desmond, K. Macapagal, and B. Mustanski. 2017. "Facilitators and Barriers to Participation in PrEP HIV Prevention Trials Involving Transgender Male and Female Adolescents and Emerging Adults." *AIDS Education and Prevention* 29(3): 205–217.

Fisher, C. B. and D. M. Layman. 2018. "Genomics, Big Data, and Broad Consent: A New Ethics Frontier for Prevention Science." *Prevention Science* 19(7): 871–879.

Franks, J., Y. Hirsch-Moverman, A. S. Loquere, K. R. Amico, R. M. Grant, B. J. Dye, Y. Rivera, R. Gamboa, and S. B. Mannheimer. 2018. "Sex, PrEP, and Stigma: Experiences with HIV Pre-Exposure Prophylaxis among New York City MSM Participating in the HPTN 067/Adapt Study." *AIDS and Behavior* 22(4): 1139–1149.

Gelinas, L., E. A. Largent, I. G. Cohen, S. Kornetsky, B. E. Bierer, and H. Fernandez Lynch. 2018. "A Framework for Ethical Payment to Research Participants." *New England Journal of Medicine* 378(8): 766–771.

Grady, C. 2006. "Ethics of International Research: What Does Responsiveness Mean?" *AMA Journal of Ethics* 8(4): 235–240.

Grant, R. M., J. R. Lama, P. L. Anderson, V. McMahan, A. Y. Liu, L. Vargas, P. Goicochea, M. Casapía, J. V. Guanira-Carranza, and M. E. Ramirez-Cardich. 2010. "Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men." *New England Journal of Medicine* 363(27): 2587–2599.

Gray, R. H., G. Kigozi, D. Serwadda, F. Makumbi, S. Watya, F. Nalugoda, N. Kiwanuka, L. H. Moulton, M. A. Chaudhary, and M. Z. Chen. 2007. "Male Circumcision for HIV Prevention in Men in Rakai, Uganda: A Randomised Trial." *The Lancet* 369(9562): 657–666.

Haire, B. and C. Jordens. 2015. "Mind the Gap: An Empirical Study of Post-Trial Access in HIV Biomedical Prevention Trials." *Developing World Bioethics* 15(2): 85–97.

Haire, B. G. and J. M. Kaldor. 2018. "Communities Need to Be Equal Partners in Determining Whether Research Is Acceptable." *Journal of Medical Ethics* 44(3): 159–160.

Office of HIV/AIDS Network Coordination (HANC). 2014a. *Native American Engagement in HIV Clinical Research: Project Guidance and Best Practices*. Seattle, WA. Available at: https://www.hanc.info/resources/Legacy%20Project%20Intiatives%20Library/NAEHCR%20Guidance%20and%20Best%20Practices%20v1.0.pdf.

Office of HIV/AIDS Network Coordination (HANC). 2014b. *Recommendations for Community Engagement in HIV/AIDS Research: A Guide for Communities and Researchers Version 2.0*. Seattle, Washington. Available at: https://www.hanc.info/cp/resources/Documents/Recommendations%202014%20FINAL%206-5-14%20rc.pdf.

Huang, Y., S. T. Karuna, H. Janes, N. Frahm, M. Nason, P. T. Edlefsen, J. G. Kublin, L. Corey, M. J. McElrath, and P. B. Gilbert. 2015. "Use of Placebos in Phase 1 Preventive HIV Vaccine Clinical Trials." *Vaccine* 33(6): 749–752.

Jacobson, N., A. Krupp, and B. J. Bowers. 2016. "Planning for Ancillary Care Provision: Lessons from the Developing World." *Journal of Empirical Research on Human Research Ethics* 11(2): 129–134.

Joint United Nations Programme on HIV/AIDS (UNAIDS). 2010. *Global Report: UNAIDS Report on the Global AIDS Epidemic 2010*. Available at: https://www.unaids.org/globalreport/documents/20101123_GlobalReport_full_en.pdf.

Joint United Nations Programme on HIV/AIDS (UNAIDS). 2017. *Start Free, Stay Free, AIDS Free: 2017 Progress Report*. Available at: https://www.unaids.org/sites/default/files/media_asset/JC2923_SFSFAF_2017progressreport_en.pdf.

Joint United Nations Programme on HIV/AIDS (UNAIDS). 2018. "AIDSinfo." Available at: http://aidsinfo.unaids.org.

Joint United Nations Programme on HIV/AIDS (UNAIDS) and AVAC. 2011. *Good Participatory Practice: Guidelines for Biomedical HIV Prevention Trials 2011*. Available at: http://www.unaids.org/sites/default/files/media_asset/JC1853_GPP_Guidelines_2011_en_0.pdf.

Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO). 2012. *Ethical Considerations in Biomedical HIV Prevention Trials (Additional Guidance Point Added 2012)*. Available at: https://www.unaids.org/sites/default/files/media_asset/jc1399_ethical_considerations_en_0.pdf.

Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization. 2013. *Guiding Principles on Ethical Issues in HIV Surveillance*. Available at: https://apps.who.int/iris/bitstream/handle/10665/90448/9789241505598_eng.pdf?sequence=1&isAllowed=y.

Jenkins Hall, W., C. J. Sun, A. E. Tanner, L. Mann, J. Stowers, and S. D. Rhodes. 2017. "HIV-Prevention Opportunities with GPS-Based Social and Sexual Networking Applications for Men Who Have Sex with Men." *AIDS Education and Prevention* 29(1): 38–48.

Kennedy, C. E., S. D. Baral, R. Fielding-Miller, D. Adams, P. Dludlu, B. Sithole, V. A. Fonner, Z. Mnisi, and D. Kerrigan. 2013. "'They Are Human Beings, They Are Swazi': Intersecting Stigmas and the Positive Health, Dignity and Prevention Needs of HIV-Positive Men Who Have Sex with Men in Swaziland." *Journal of the International AIDS Society* 16: 18749.

Kong, M., Z. Li, J. Wu, J. Hu, Y. Sheng, D. Wu, Y. Lin, M. Li, X. Wang, and S. Wang. 2019. "A Wearable Microfluidic Device for Rapid Detection of HIV-1 DNA Using Recombinase Polymerase Amplification." *Talanta* 205: 120155.

Krakower, D. S., S. Gruber, K. Hsu, J. T. Menchaca, J. C. Maro, B. A. Kruskal, I. B. Wilson, K. H. Mayer, and M. Klompas. 2019. "Development and Validation of an Automated HIV Prediction Algorithm to Identify Candidates for Pre-Exposure Prophylaxis: A Modelling Study." *The Lancet* HIV 6(10): e696–e704.

Lancaster, K. E., I. F. Hoffman, B. Hanscom, T. V. Ha, K. Dumchev, H. Susami, S. Rose, V. F. Go, S. A. Reifeis, and K. R. Mollan. 2018. "Regional Differences between People Who Inject Drugs in an HIV Prevention Trial Integrating Treatment and Prevention (HPTN 074): A Baseline Analysis." *Journal of the International AIDS Society* 21(10): e25195.

Leitner, T. and E. Romero-Severson. 2018. "Phylogenetic Patterns Recover Known HIV Epidemiological Relationships and Reveal Common Transmission of Multiple Variants." *Nature Microbiology* 3(9): 983.

London, A. J. and J. Kimmelman. 2008. "Justice in Translation: From Bench to Bedside in the Developing World." *The Lancet* 372(9632): 82-85.

Luna, F. 2019. "Identifying and Evaluating Layers of Vulnerability–A Way Forward." *Developing World Bioethics* 19(2):86–95.

Luna, F. 2019. "Identifying and Evaluating Layers of Vulnerability–A Way Forward." *Developing World Bioethics* 19(2):86–95.

Lyerly, A. D. 2019. "Dolutegravir: Advancing Ethical Research in Pregnancy." *The Lancet* 394(10213): 1972–1974.

Lyerly, A. D., M. O. Little, and R. Faden. 2008. "The Second Wave: Toward Responsible Inclusion of Pregnant Women in Research." *International Journal of Feminist Approaches to Bioethics* 1(2): 5–22.

MacQueen, K. and M. May. 2008. *Partnering for Care in HIV Prevention Trials: A How-to Manual*. Durham, NC: Family Health International.

MacQueen, K. M. and J. D. Auerbach. 2018. "It Is Not Just About 'the Trial': The Critical Role of Effective Engagement and Participatory Practices for Moving the HIV Research Field Forward." *Journal of the International AIDS Society* 21(Suppl Suppl 7).

MacQueen, K. M. and W. Cates, Jr. 2005. "The Multiple Layers of Prevention Science Research." *American Journal of Preventive Medicine* 28(5): 491–495.

MacQueen, K. M. and Q. A. Karim. 2007. "Practice Brief: Adolescents and HIV Clinical Trials: Ethics, Culture, and Context." *Journal of the Association of Nurses in AIDS Care* 18(2): 78–82.

MacQueen, K. M., Q. A. Karim, and J. Sugarman. 2003. "Ethics Guidance for HIV Prevention Trials." *BMJ* 327(7410): 340.

Marcus, J. L., L. B. Hurley, D. S. Krakower, S. Alexeeff, M. J. Silverberg, and J. E. Volk. 2019. "Use of Electronic Health Record Data and Machine Learning to Identify Candidates for HIV Pre-Exposure Prophylaxis: A Modelling Study." *The Lancet HIV* 6(10): e688–e695.

Merritt, M. W., J. Katz, R. Mojtabai, and K. P. West, Jr. 2015. "Referral of Research Participants for Ancillary Care in Community-Based Public Health Intervention Research: A Guiding Framework." *Public Health Ethics* 9(1): 104–120.

Mngadi, K. T., J. A. Singh, L. E. Mansoor, and D. R. Wassenaar. 2017. "Undue Inducement: A Case Study in Caprisa 008." *Journal of Medical Ethics* 43(12): 824–828.

Montgomery, E. T., M. Beksinska, N. Mgodi, J. Schwartz, R. Weinrib, E. N. Browne, N. Mphili, P. Musara, M. Jaggernath, and S. Ju. 2019. "End-User Preference for and Choice of Four Vaginally Delivered HIV Prevention Methods among Young Women in South Africa and Zimbabwe: The Quatro Clinical Crossover Study." *Journal of the International AIDS Society* 22(5): e25283.

Mooney, S. J., D. J. Westreich, and A. M. El-Sayed. 2015. "Epidemiology in the Era of Big Data." *Epidemiology* 26(3): 390.

Multi-Regional Clinical Trials •(MRCT). 2017. 2017 *Impact Report: Harmonizing the Clinical Trial Ecosystem*. Cambridge, MA: The MRCT Center of Brigham and Women's Hospital and Harvard. Available at: https://mrctcenter.org/wp-content/uploads/2017/12/MRCT_2017_IMPACT_report_Web.pdf.

Mugwanya, K. K., E. Irungu, E. Bukusi, N. R. Mugo, J. Odoyo, E. Wamoni, K. Ngure, J. F. Morton, K. Peebles, and S. Masyuko. 2018. "Scale up of PrEP Integrated in Public Health HIV Care Clinics: A Protocol for a Stepped-Wedge Cluster-Randomized Rollout in Kenya." *Implementation Science* 13(1): 118.

National Academies of Sciences Engineering and Medicine (NASEM). 2018. *Returning Individual Research Results to Participants: Guidance for a New Research Paradigm*. National Academies Press. Available at: http://www.nationalacademies.org/hmd/Reports/2018/returning-individual-research-results-to-participants.aspx.

Newman, P. A., C. Rubincam, C. Slack, Z. Essack, V. Chakrapani, D.-M. Chuang, S. Tepjan, M. Shunmugam, S. Roungprakhon, and C. Logie. 2015. "Towards a Science of Community Stakeholder Engagement in Biomedical HIV Prevention Trials: An Embedded Four-Country Case Study." *PLoS One* 10(8): e0135937.

Pallmann, P., A. W. Bedding, B. Choodari-Oskooei, M. Dimairo, L. Flight, L. V. Hampson, J. Holmes, A. P. Mander, M. R. Sydes, and S. S. Villar. 2018. "Adaptive Designs in Clinical Trials: Why Use Them, and How to Run and Report Them." *BMC Medicine* 16(1): 29.

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

Paul, A., M. W. Merritt, and J. Sugarman. 2018. "Implementing Post-Trial Access Plans for HIV Prevention Research." *Journal of Medical Ethics* 44(5): 354–358.

President's Emergency Plan for AIDS Relief (PEPFAR). 2012. *Capacity Building and Strengthening Framework*. Washington, DC: Office of the U.S. Global AIDS Coordinator and Health Diplomacy. Available at: https://www.pepfar.gov/documents/organization/197182.pdf.

Rennie, S. and J. Sugarman. 2010. "Developing Ethics Guidance for HIV Prevention Research: The HIV Prevention Trials Network Approach." *Journal of Medical Ethics* 36(12): 810–815.

The Research Fairness Institute (RFI). 2018. *RFI Summary Guide*. Available at: http://rfi.cohred.org/wp-content/uploads/2018/04/RFI_SummaryGuide_EN_v2.0_20180315.pdf

Richardson, H. S. 2007. "Gradations of Researchers' Obligation to Provide Ancillary Care for HIV/AIDS in Developing Countries." *American Journal of Public Health* 97(11): 1956–1961.

Richardson, H. S. and L. Belsky. 2004. "The Ancillary-Care Responsibilities of Medical Researchers: An Ethical Framework for Thinking about the Clinical Care That Researchers Owe Their Subjects." *Hastings Center Report* 34(1): 25–33.

Robinson, E. T., D. Baron, L. L. Heise, J. Moffett, and S. V. Harlan. 2010. *Communications Handbook for Clinical Trials*. Durham, NC: Family Health International.

SRHR Africa Trust (SAT). 2017. Age of Consent. *Global Analysis*. Available at: https://www.trust.org/contentAsset/raw-data/b4e4a24b-f66d-4170-aa46-6713e038e139/file.

Shah, S., R. Wolitz, and E. Emanuel. 2013. "Refocusing the Responsiveness Requirement." *Bioethics* 27(3): 151–159.

Shah, S. K., J. Kimmelman, A. Lyerly, H. Lynch, F. Miller, R. Palacios, C. Pardo, and C. Zorrilla. 2018. "Bystander Risk, Social Value, and Ethics of Human Research." *Science* 360(6385): 158–159.

Singh, J. A. 2017. "Ethical and Legal Considerations for Realising Post-Trial Access of Novel Experimental Interventions: Lessons from the Caprisa 004 Trial." In Q. Abdool Karim, S. Abdool Karim, and C. Baxter (eds) *The Caprisa Clinical Trials: HIV Treatment and Prevention*. Springer, Cham, 191–200.

Smithers, N. 2011. *The Importance of Stakeholder Ownership for Capacity Development Results*. World Bank Institute Capacity Development and Results. Washington, D.C.: World Bank Group.

Sugarman, J. 2017. "Examining Provisions Related to Consent in the Revised Common Rule." *The American Journal of Bioethics* 17(7): 22–26.

Sugarman, J., M. Barnes, S. Rose, K. Dumchev, R. Sarasvita, H. T. Viet, O. Zeziulin, H. Susami, V. Go, and I. Hoffman. 2018. "Development and Implementation of Participant Safety Plans for International Research with Stigmatised Populations." *The Lancet HIV* 5(8): e468–e472.

Sugarman, J., C. L. Celum, D. Donnell, and K. H. Mayer. 2019. "Ethical Considerations for New HIV Prevention Trials." *The Lancet HIV* 6(8): e489–e491.

Sugarman, J., S. M. Rose, and D. Metzger. 2014. "Ethical Issues in HIV Prevention Research with People Who Inject Drugs." *Clinical Trials* 11(2): 239–245.

Taylor, D., C. Lunny, P. Lolić, O. Warje, J. Geldman, T. Wong, M. Gilbert, R. Lester, and G. Ogilvie. 2019. "Effectiveness of Text Messaging Interventions on Prevention, Detection, Treatment, and Knowledge Outcomes for Sexually Transmitted Infections (STIs)/HIV: A Systematic Review and Meta-Analysis." *Systematic Reviews* 8(1): 12.

van der Straten, A., J. Stadler, E. Montgomery, M. Hartmann, B. Magazi, F. Mathebula, K. Schwartz, N. Laborde, and L. Soto-Torres. 2014. "Women's Experiences with Oral and Vaginal Pre-Exposure Prophylaxis: The VOICE-C Qualitative Study in Johannesburg, South Africa." *PloS One* 9(2): e89118.

Vayena, E., M. Salathé, L. C. Madoff, and J. S. Brownstein. 2015. Ethical Challenges of Big Data in Public Health. *PLoS Computational Biology* 11(2): e1003904.

Vaz, L., A. Corneli, J. Dulyx, S. Rennie, S. Omba, F. Kitetele, A. R. Group, and F. Behets. 2008. "The Process of HIV Status Disclosure to HIV-Positive Youth in Kinshasa, Democratic Republic of the Congo." *AIDS Care* 20(7): 842–852.

Weijer, C., G. Goldsand, and E. J. Emanuel. 1999. "Protecting Communities in Research: Current Guidelines and Limits of Extrapolation." *Nature Genetics* 23(3): 275.

Wendler, D. and J. Rackoff. 2002. "Consent for Continuing Research Participation: What Is It and When Should It Be Obtained?" *IRB* 24(3): 1.

Wenner, D. M. 2017. "The Social Value of Knowledge and the Responsiveness Requirement for International Research." *Bioethics* 31(2): 97–104.

World Health Organization (WHO). 2015. *WHO Expands Recommendation on Oral Pre-Exposure Prophylaxis of HIV Infection (PrEP)*. Policy brief. Geneva: WHO.

World Health Organization (WHO). 2018. *Guidance on Ethical Considerations in Planning and Reviewing Research Studies on Sexual and Reproductive Health in Adolescents*. Available at: https://apps.who.int/iris/bitstream/handle/10665/273792/9789241508414-eng.pdf?ua=1.

Woodcock, J. and L. M. LaVange. 2017. "Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both." *New England Journal of Medicine* 377(1): 62–70.

World Medical Association. 2013. *World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

Young, S. D., W. Yu, and W. Wang. 2017. "Toward Automating HIV Identification: Machine Learning for Rapid Identification of HIV-Related Social Media Data." *Journal of Acquired Immune Deficiency Syndromes* (1999) 74(Suppl 2): S128–S131.

GLOSSARY

Ancillary care: care that participants may need but the reason for providing the care is not related to the scientific objectives of the research nor to address research-related injury.

Assent: an agreement to take part in research or research procedures that is typically used in research with children or minors, which does not have the same significance or standards as consent.

Bystander: a non-participant in research who is affected by it.

Clinical equipoise: a situation in which expert opinion is divided on the question about whether one arm of a clinical trial is superior to another.

Common Rule: the US Federal policy for the protection of human research subjects.

Ethical aspiration: implies that following the course of action is a matter of pursuing important ethical ideals and is desirable but not required.

Ethical obligation: normally the action should be done, and while exceptions to that course of action are sometimes permissible, these exceptions require a strong ethical justification.

Post-trial access: provision of or access to an investigational product after research ends.

Prevention package: a collection of services for human immunodeficiency virus (HIV) prevention made available to all participants in an HIV prevention research project.

Research concept: a brief description of an idea for a possible research project.

Research sites: the locations where research actually occurs.

Responsiveness: addressing research questions that are locally relevant and reflect host communities' health priorities.

Sponsor: an entity that funds a clinical trial.

Stakeholders: people or organizations who have an interest in research or are affected by its outcomes.

Study team: the individuals working on the research project.

Undue influence: an influence that causes someone to make an unreasonable choice given their values and interests.