

UNAIDS 2021

Ethical considerations in HIV prevention trials

UNAIDS and WHO guidance document

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Foreword

HIV prevention is vital to ending the AIDS epidemic.

Over more than 30 years, HIV research has identified many safe and effective prevention modalities, including male and female condom use, viral load suppression in people living with HIV, harm reduction programmes for people who inject drugs, pre- and post-exposure prophylaxis, and voluntary medical male circumcision. The behavioural, structural and societal aspects of HIV prevention are increasingly understood, and responsive interventions have been defined.

While the range and use of HIV prevention methods are increasing, they remain insufficient. An estimated 1.7 million people acquired HIV in 2019. There is therefore an urgent need to develop and make available more appropriate, highly effective and long-term HIV prevention solutions.

Research on human subjects is governed by a well-established framework of ethical standards. This revision of the joint UNAIDS and World Health Organization ethical guidance for HIV prevention research upholds and explains universal ethical principles for research involving humans, in ways that are relevant to participating people and populations and responsive to developments in HIV prevention research. The result of extensive consultation, this guidance draws on previous ethical guidance documents and the HIV movement's commitment to equality, non-discrimination, community support and social justice in order to outline the characteristics of ethically responsible HIV prevention research.

Current and future HIV prevention research—and the accompanying ethical considerations—are increasingly complex for several reasons. Firstly, research into prevention methods should be conducted with the populations where they might have the most impact. This includes key populations and adolescent girls and young women in contexts with a high incidence of HIV infection. Members of these populations however, often live in societal or political contexts of vulnerability that limit their participation and challenge ethical research conduct. Secondly, providing all of the recommended HIV prevention modalities to study participants reduces HIV incidence in the study population and makes it more difficult to demonstrate a prevention effect of an experimental intervention. This leads to the adaptation of study designs and new patterns of participant recruitment that were not addressed in the previous ethical research guidance.

The HIV prevention goal set in the United Nations 2016 Political Declaration on Ending AIDS is to reduce new HIV infections to less than 200 000 by 2030. To this end, UNAIDS and WHO strongly support all valid approaches to improving HIV prevention technology, provision and use, while also recognizing their role in promoting the rights of populations affected by HIV. This revised guidance can be used to support all stakeholders in designing and conducting ethically and scientifically sound HIV prevention trials that advance the response towards the 2030 HIV prevention goal.

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Guidance points

Guidance Point 1: the necessity for HIV prevention trials

There is an urgent need for additional, safe, more effective and more acceptable HIV prevention methods, due to insufficient progress in reducing new HIV infections, absence of a vaccine or a cure and the human, public health, social and economic severity of the HIV epidemic. Developing HIV prevention methods should improve the health and welfare of the communities involved in research and also benefit the wider population at risk of HIV acquisition or transmission. All relevant stakeholders—such as representatives from affected communities, civil society organizations, trial sponsors and researchers, research institutions, industry, public health authorities, regulators, development partners, funding agencies, governments and international organizations—should work together to foster the timely, scientifically sound and ethically responsible development of safe, effective and acceptable HIV prevention methods and improvements to existing ones. Researchers and sponsors—in partnership with the participating community, regulatory and governmental authorities and pharmaceutical manufacturers—must agree on a clear development plan in advance of the conduct of the research that ensures that any trial addresses the pathway and necessary means towards access to a new HIV prevention method.

Guidance Point 2: community partnership

Research teams and trial sponsors must partner with key stakeholders—including key populations, potential participants and their communities, and researchers—from settings and populations where trials are taking place or are planned. These partnerships must be formed in a transparent and meaningful participatory process of trial design, implementation and follow-up that involves all stakeholders as equal partners. Key stakeholders and communities should be involved from the outset in the design, development, implementation and dissemination of results of HIV prevention trials. Researchers and trial sponsors must invest sufficient resources to enable such participation and to ensure good participatory practice.

Guidance Point 3: scientific and ethics conduct and review

HIV prevention trials in all phases and all geographic locations should be conducted only if adequate scientific and clinical capacity and ethics safeguards can be ensured in the setting where the research is to be carried out. The safeguards must include independent and competent scientific and ethics review. In settings where capacity for scientific and ethics review and conduct is limited, relevant stakeholders should collaborate to strengthen and build capacity for scientific and ethics conduct and review oversight processes. Proposed HIV prevention trial protocols should be reviewed by scientific and ethics review committees that are located in, and include membership from, the countries in which the research will be conducted and in

which the principal researchers are based. For HIV prevention trials that involve multiple countries or trial sites, the research collaboration should endeavour to build equal partnerships, allowing for optimal use of resources and knowledge, capacity-strengthening and the highest standards of research integrity.

Guidance Point 4: scientific validity

All HIV prevention research must be scientifically valid. The methodology employed to define and answer the question should be rigorous. In order to ensure scientifically valid results, researchers must clearly articulate in the protocol the products to be tested, the results of previous animal and human testing phases (if relevant), justification of the trial design, justification for any placebo, choice of control and experimental arms, trial endpoints and methodology for statistical analyses. The research question, trial design and statistical analyses should represent current best practices, conform to relevant regulatory standards and be of relevance to local research settings and communities.

Guidance Point 5: fair and inclusive selection of study populations

The selection of study populations and communities from which participants will be recruited must be fair and scientifically justified and transparent. Protocols must have a recruitment plan with relevant information about the proposed study populations to be recruited and who the end users of the intervention are likely to be. Interventions should be tested in the populations likely to use them. In addition, product development plans should strive for broad use across populations at risk. Researchers, trial sponsors and research ethics committees must not arbitrarily exclude persons and populations on the basis of characteristics such as age (including children and adolescents), race or ethnicity, pregnancy, lactation or child-bearing potential, involvement in sex work, substance use, sexual orientation, disability, incarceration, gender identity or coinfections and comorbidities. Such arbitrary exclusion can result in trial results being less impactful as they exclude the people who would most benefit from them or exacerbate health disparities and may impact on the roll-out of effective products to at risk individuals and groups.

Guidance Point 6: social and political contexts of vulnerability

The people who could significantly benefit from new, safe and effective HIV prevention interventions often live in social or political contexts of vulnerability to exploitation, prosecution or other harms. Researchers, trial sponsors and research ethics committees

should be mindful of people and populations living in these contexts when establishing the safety, efficacy and effectiveness of interventions and when maximizing the benefits of future successful HIV prevention options that can be useful specifically for the people and populations that can most benefit from them. Researchers and trial sponsors should work with communities and relevant civil society stakeholders to overcome legal, ethical, regulatory and other challenges to the research participation of populations living in these contexts. Researchers and trial sponsors should take measures to protect the safety, dignity, human rights and welfare of participants, and to prevent discrimination or prejudice. Researchers and trial sponsors must recognize that participation in research may also increase the risk of social, psychological or legal harms for participants, including through inadvertent disclosure of information, stigmatization and discrimination and take adequate measures to prevent and/or mitigate such harms.

Guidance Point 7: potential harms

Researchers must specify as fully as possible in protocols and informed consent documents the nature, magnitude and probability of harms to both participants and others that may result from the intervention and procedures. These harms may include physical harms, discomfort and side-effects, social, economic, legal and psychological impacts. Study protocols and informed consent documents should explicitly specify how potential study-related harms will be managed. The protocol must specify the plans to minimize, mitigate and remedy these potential harms. Potential harms must be appropriately balanced in relation to the anticipated individual and societal benefits of the research.

Guidance Point 8: benefits

Researchers must provide an accurate statement in protocols and informed consent documents of the anticipated benefits that may result to participants and others from the intervention and procedures. These may include physical, societal, economic, and psychological benefits. The protocol should outline any services, products and other ancillary interventions provided in the course of the research that are likely to benefit participants in the trials, including arrangements to refer for care or other services. Such benefits should not be presented in a manner that unduly influences freedom of choice regarding research participation.

Guidance Point 9: informed consent

Research teams and trial sponsors should ensure that participants provide voluntary informed consent based on adequate, accurate and appropriately conveyed and understood information before enrolment, as laid out in international ethical guidance documents. Specific measures should be taken to support and protect persons who are, or who may be, limited in their ability to participate voluntarily or provide informed consent. Participants have a right to refuse to participate or withdraw at any point in the trial without negative consequences. For trials involving children, the permission of a parent or legal guardian is generally required along with the assent of the child, unless strict requirements for parental waiver can be met. Separate informed consent should be sought for procedures that are beyond the activities described in the protocol, for example data banking and biobanking.

Guidance Point 10: confidentiality and privacy

Researchers have an ongoing obligation to participants to develop and implement stringent procedures and systems to maintain the confidentiality and security of personal information, including information collected during a trial and after its completion. Researchers should assess the privacy risks for participants, mitigate these risks as much as possible and describe the remaining risks in the protocol.

Guidance Point 11: standard of prevention

Researchers and trial sponsors should, at a minimum, ensure access to the package of prevention methods recommended by the WHO for every participant throughout the trial and follow-up, including during any pre-enrolment or “run-in” period prior to randomization, and in cohort studies set up to establish the feasibility of subsequent prevention trials. A departure from the WHO-recommended standard can be justified only if relevant stakeholders, inclusive of community stakeholders, are meaningfully engaged and accept a compelling scientific or biological rationale for the departure from the standard. Any such departure from the standard should be explicitly approved by the research ethics committee. When new HIV prevention methods are scientifically validated and recommended by WHO, they should be added to the standard of prevention as soon as is practically possible based on consultation among relevant stakeholders, including community stakeholders. The uptake of and adherence to components of the standard prevention package should be monitored actively by the trial team and other stakeholders while the trial is ongoing.

Guidance Point 12: care and treatment

Researchers and sponsors should ensure linkage to treatment programmes in line with WHO guidance for optimal treatment for all participants who test positive for HIV infection during screening or who acquire HIV during the trial. Plans for access to the optimal national standard of HIV-related care and treatment must be explicit in the protocol and should include drug resistance testing.

Guidance Point 13: trial monitoring

Researchers and sponsors should ensure that monitoring throughout the duration of the trial covers the ethical requirements of research with humans. These requirements include, but are not limited to, safety and efficacy of the interventions, the initial and continuing quality of the informed consent process and confidentiality of data, access to WHO-recommended prevention methods and to WHO-recommended care and treatment for those who test positive for HIV infection during screening or who acquire HIV during the trial.

Guidance Point 14: post-trial access and dissemination

As part of the protocol, researchers and trial sponsors should have an agreed plan for post-trial access. In principle, trial sponsors should provide ongoing provision of HIV preventive products that have been demonstrated to be efficacious to all trial participants. The research team also has a special obligation to ensure the timely dissemination of study progress at regular intervals and to report and publish the final results in peer-reviewed journals. Dissemination of progress updates and results to national authorities, local communities and study participants should be a priority and occur before or contemporaneously with international dissemination.

Introduction

UNAIDS is a cosponsored Joint Programme in the United Nations (UN) system. It draws on the experience and expertise of 11 UN Cosponsors. Civil society is represented on its governing body. UNAIDS is leading the global effort to end AIDS as a public health threat. The World Health Organization (WHO) is one of its Cosponsors and works worldwide to promote health, keep the world safe and serve the vulnerable.

The first version of the UNAIDS/WHO guidance document (2000)

Following deliberations during 1997–99 involving participants from 33 countries—including lawyers, activists, social scientists, ethicists, vaccine scientists, epidemiologists, representatives of nongovernmental organizations, people living with HIV and people working in health policy—UNAIDS published a guidance document on ethical considerations in HIV preventive vaccine research in 2000.

The second version of the UNAIDS/WHO guidance document (2007/2012)

The revision of the 2000 guidance document incorporated developments that had taken place since the original publication, including lessons learned in the field of HIV prevention research. Many different strategies for HIV prevention were being explored, including microbicides, vaccines, female-initiated barrier methods, herpes simplex virus type 2 treatment and suppression, index partner treatment, antiretroviral pre-exposure prophylaxis (PrEP), prevention of mother-to-child transmission of HIV, viral hepatitis and syphilis, opioid substitution therapy and maintenance for injecting drug users. Following the compelling evidence of a 50–60% reduction in HIV acquisition from voluntary medical male circumcision (VMMC) in three randomized controlled trials in Kenya, South Africa and Uganda, WHO and UNAIDS produced recommendations in 2007 judging voluntary medical male circumcision to be an accepted HIV prevention measure in men in high-prevalence, generalized HIV epidemics in which heterosexual transmission predominates.

In 2012, a guidance point on the ethical engagement of people who inject drugs was added, since it had been identified that the existing guidance documents did not consider with enough specificity the challenges of engaging people who inject drugs in biomedical HIV prevention trials and other HIV prevention research.

The third version of the UNAIDS/WHO guidance document (2020)

A revision of the 2012 version was essential for a number of reasons, including the recent availability of PrEP and the expected development of other highly effective HIV prevention tools. Although previous versions of the guidance anticipated improvement in HIV prevention tools, they did not explicitly consider the possibility of highly effective HIV prevention being made available to research participants and the consequences of this for trial design, costs and ethical standards. A further reason to undertake the revision is the need to involve in prevention research populations with a continuing high incidence of HIV infection. These populations stand to benefit from new HIV prevention methods that are better suited to their needs, but they also may be in need of special ethical protections if they are in social or political contexts of vulnerability.

Revision process for the 2020 version

In order to revise the UNAIDS/WHO guidance, a reflective equilibrium approach was used, going back and forth between scientific insights, methodology, normative principles, and internal and public discussion in order to reach a consensus. The revision started with a plenary meeting of 79 participants in Montreux, Switzerland, on 20–22 November 2019. This group consisted of experts and representatives of civil society, communities with an increased risk of acquiring HIV infection, regulatory authorities and manufacturers, prevention researchers and trial designers, trial sponsors and other relevant funders, biostatisticians and ethicists. Several members of the previous working group for the development of the 2007 version of the guidance were also present.

Prior to the meeting, participants were asked to make personal scores of how consistent with recent advances they found each of the current guidance points. Through this scoring, guidance on standard of prevention, control groups, availability of outcomes and clinical trial phases were identified as important candidates for revision. Furthermore, guidance on special populations—such as women, children and people who inject drugs—needed revision. Lower priority for revision was assigned to guidance on informed consent, community participation and confidentiality.

On days 1 and 2 of the meeting, presentations by various expert stakeholders helped the participants reflect on the guidance points that needed revision. On the second day, breakout groups were asked to develop a first proposal for revision. At the end of day 2, the proposed wording was refined into a first draft. Some draft guidance points were consolidated, and a new point was created covering scientific validity. On day 3, the breakout groups worked on refining the first draft. Only the 44 participants with no

reported significant conflicts of interest were present on this day, in accordance with WHO guidance.

From November to December 2019, the Steering Committee prepared a first draft of the guidance points, which they forwarded to the participants of the Montreux meeting for further input. The participants were able to send comments back to the Steering Committee, which prepared a new draft based on the comments. In February 2020, the document was sent for public consultation to meeting participants and a wider public through invitations to relevant networks. Commentators also provided declarations of interest, which were reviewed in line with WHO standard procedures.

After comments were received, the Steering Committee prepared a final version of the guidance points and a revision of the commentaries on the guidance points. Following this revision, meeting participants from the November 2019 meeting were sent the revision in November 2020 and asked for comments. Based on their comments, this version was finalized.

Aims and scope of the guidance document

This guidance document has the following starting points:

1. The guidance points in this document should be read and understood as a whole.
2. The guidance points are generic: each trial will require interpretation and application of the guidance points.
3. The consultation, conception, planning, conduct, and implementation of HIV prevention trials is done by appropriately qualified researchers, sponsors, communities and other key stakeholders who have committed to carrying out research that confirms to international, ethical, procedural and confidentiality standards.

UNAIDS and WHO have taken guidance and advice from stakeholders during the meeting and public consultation to provide improved, updated guidance for the ethical, safe and effective planning and conduct of HIV prevention trials. This document focuses on new tools for primary prevention of HIV infection. The scope of this document does not include trials to prevent mother-to-child transmission of HIV, nor does it include studies of the impact of treatment or other interventions for prevention delivered to people living with HIV. The scope of this document is specific to novel biomedical tools and does not include trials of structural, social, health system or behavioural interventions. At the same time, many of the guidance points and discussions remain relevant to these areas of research. Where UNAIDS and WHO feel that these elements are adequately addressed by other texts, there has been no attempt made to duplicate or replace them; rather, they should be consulted extensively throughout HIV prevention product development activities. These texts include the following:

- ▶ *The Nuremberg Code (1947).*
- ▶ *The Belmont report (1979).*
- ▶ *The ethics of research related to healthcare in developing countries* from the Nuffield Council on Bioethics (2002).
- ▶ *The handbook for good clinical research practice* from WHO (2005).

- ▶ The Universal Declaration on Bioethics and Human Rights from the United Nations Educational, Scientific and Cultural Organization (UNESCO) (2005).
- ▶ The interim *Guidelines on protecting the confidentiality and security of HIV information* by UNAIDS (2007).
- ▶ *Good participatory practice: guidelines for biomedical HIV prevention trials* by UNAIDS (2011).
- ▶ The Declaration of Helsinki by the World Medical Association (2013).
- ▶ The *International ethical guidelines for health-related research involving humans* by the Council for International Organizations of Medical Sciences (CIOMS) (and developed in collaboration with WHO) (2016).
- ▶ The *Guideline for good clinical practice E6(R2)* by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (2016).
- ▶ *The privacy, confidentiality and security assessment tool* by UNAIDS (2019).
- ▶ *The privacy, confidentiality and security assessment tool: user manual* by UNAIDS (2019).

It is hoped that this document will be of use to all partners who develop, conduct, review, participate in and facilitate appropriate trials of HIV prevention. These partners include (but are not limited to) potential research participants, investigators, research staff, community members, government representatives, regulators, funders, pharmaceutical companies and other industry partners, trial sponsors, and ethical and scientific review committees involved in the development of HIV prevention products and interventions. This revised guidance suggests standards—and processes for arriving at standards—that can be used as a frame of reference for conducting further discussion at the local, national and international levels, and it can inform the development of national guidance for the conduct of HIV prevention trials in an ethical manner. The ultimate decision for ethics approval rests with research ethics committees, predominantly at the local level.

Context

The HIV pandemic is characterized by unique biological, social and geographical factors that, among other things, affect the balance of risks and benefits for individuals and communities who participate in HIV prevention trials. These factors may require that additional efforts be made to address the needs of participating individuals and communities. People at risk of HIV or living with HIV urgently need to have access to a tailored package of optimal HIV prevention interventions that changes with their needs throughout their life cycle, a need to have their rights protected and their welfare promoted in the context of the development and testing of novel HIV prevention modalities and combinations, and a need to be able to participate fully as equal participants in the research process. The current challenge is to ensure progress in HIV prevention research in an ethically responsible manner.

The number of people living with HIV continues to increase. In 2019, 1.7 million people newly acquired HIV and 690 000 people died from AIDS-related causes. Currently available treatments do not lead to a cure, but they can halt the progression of disease and eliminate the risk of HIV transmission between a person living with HIV and an HIV-negative person. Effective treatment for HIV with antiretroviral medications is lifelong, which requires care, support and monitoring, is still costly (especially for second-line regimens), and can cause significant adverse effects. In 2019, 67% (25 million people) had access to antiretroviral therapy, - more than three times as many people as in 2010.

There is therefore an ethical imperative to seek effective and accessible HIV prevention technologies as urgently as possible to complement existing prevention strategies. This ethical imperative demands that these technologies be developed to address the situation of those people and populations most vulnerable to exposure to HIV infection.

Ethical issues that this document aims to address

The following issues create ethical dilemmas that this guidance document aims to address.

Participation of populations with highest incidence

For efficacy trials of any HIV prevention product, the populations most likely to be considered for participation are those with the highest incidence of HIV and those who could significantly benefit from new, safe and effective HIV prevention interventions. Researchers and sponsors therefore need to work directly with populations in which some people are at higher risk of HIV acquisition. However, people in these populations often live in social or political contexts that render them vulnerable to exploitation, stigma, criminalization, and prosecution or other harms.

Risks to nonparticipants

In some HIV prevention trials, individuals other than the trial participants may experience risks if they are exposed to the experimental product, or they may experience benefits if the product is effective. For example, male sexual partners may be exposed to topical microbicides, and fetuses and infants may be exposed to systemic treatments given to their mothers. Nonparticipants may benefit from successful prevention of HIV infection in their sexual partners, but they also could experience risks should the intervention lead to antiretroviral resistance in their partner.

Potential imbalance between conceiving, developing and manufacturing versus testing

HIV prevention modalities may be conceived and manufactured in laboratories in one location (the sponsor country or countries; often high-income countries) and be tested in human populations in another location (including low- and middle-income countries). The potential imbalance of such a situation demands particular attention to ways to address the differing perspectives, interests and capacities of trial sponsors, countries and communities engaged in trials.

Fear and stigmatization of HIV infection

HIV infection is both highly feared and heavily stigmatized. This is in large part because it is associated with sex, sexuality, blood, death, and behaviours and people that are subject to fear and stigmatisation such as sex work, gay men and other men who have sex with men, transgender people, sexual behaviour of adolescent girls and young women, and injecting drugs or other drug use. These are issues that may be difficult to address openly at a societal and individual level; in some settings, these practices are also illegal. As a result, people living with HIV may experience stigma and discrimination and even violence, while some communities continue to deny the existence and prevalence of HIV infection or to even acknowledge stigmatized groups. Furthermore, vulnerability to HIV exposure and its impact is greater where people are marginalized due to their gender, sexuality, and/or social, economic and legal status. These factors increase the risk of social and psychological harm for people participating in HIV prevention trials.

HIV incidence in HIV prevention trials

Experience to date has shown that HIV incidence in both the experimental and control arms of HIV prevention trials may fall below the pre-trial incidence. This reduction may be as a result of sustained risk reduction counselling and access to effective HIV

prevention tools or may be for less direct social and behavioural reasons. Participation in an HIV prevention trial may therefore be of benefit to all participants, even if the experimental product is not efficacious. The statistical power of a trial to determine efficacy may also be over-estimated if based on pre-trial estimates of incidence.

Communication of combination prevention

Combination prevention emphasizes the need for structural, biomedical and behavioural interventions to prevent HIV, along with the need for individuals to choose one or more strategies at different times in their lives to reduce their risks of exposure not only to HIV, but also to other related harms or unwanted consequences of unprotected sex or harmful drug use practices. The social change communication strategies that emphasize combination prevention will be crucial to ensuring that a new HIV prevention product truly does add to the existing tools when it is introduced. Ongoing research, monitoring and surveillance will always be needed to demonstrate that the anticipated benefit of new, efficacious products is realized within the context of combination prevention.

Trial design and PrEP provision

Suitable and ethically acceptable designs need to be found for trials of new HIV prevention products that take into account the existence of highly effective prevention products such as PrEP. Failing this, the number of potentially valuable studies could be limited severely and the increased delay between identifying a potentially effective product and receiving regulatory approval could deprive people of timely access to additional HIV prevention options.

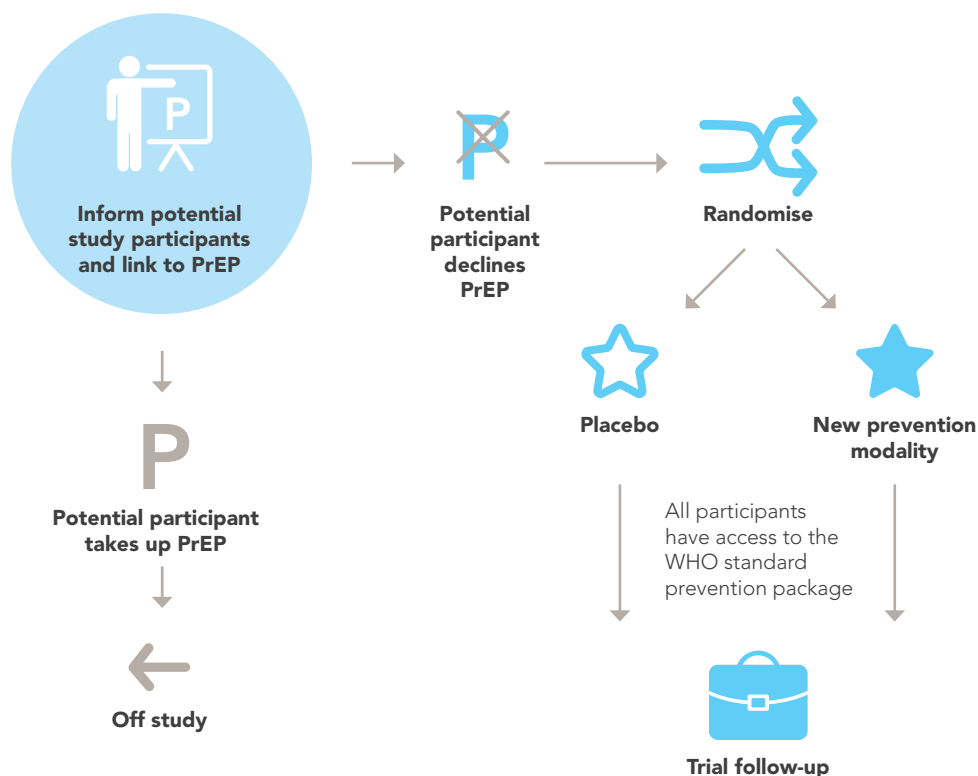
Extensive work has been undertaken on new trial designs in response to the availability of PrEP, including several current antiretroviral medicine-based trials with participants receiving tenofovir disoproxil/emtricitabine PrEP in an active control arm. Because there may be very few events (new HIV infections), confidence intervals will be wide unless the trial is impractically large. Ways of estimating a counterfactual HIV incidence for comparison are also being explored.

Vaccine- or antibody-mediated antibody trials are not currently being studied in direct comparison with PrEP, but PrEP is provided as part of the background standard of prevention. PrEP access as described in the trial protocol may be through existing local PrEP services (which may vary across the research sites of these trials), at trial sites or at a combination of these.

Another suggested approach to facilitate placebo-controlled prevention trials involves recruiting participants who are currently not willing to use PrEP, or participants from populations where PrEP adherence is known to be low despite good access to PrEP. The rationale for this “opt-out” approach (see Figure below) is that a new prevention modality—such as an implant, long-acting injection, antibody or vaccine—could be better suited to the needs of these populations, and it could be tested against a placebo (when added to the WHO standard package of prevention) even in the absence of highly effective prevention use. All trial participants would have the option to use PrEP and would be provided access to it if they chose to use it during the course of the trial.

Figure 1.

Flow diagram showing one example of how the “opt out” approach could work



Source: Adapted from Holly Janes’ presentation at the plenary Montreux meeting, November 2019.

Implications for regulatory evaluation

Evidence of efficacy and safety for regulatory review of new HIV prevention products has to meet certain standards. As trial designs become more complex, the studies still need to retain statistical power, and they should be transparently described, as should the analyses. Active liaison between product developers, regulators, researchers and community advocates early in the protocol development will help to maintain the transparency of the study design and describe the anticipated analyses of results. Harmonization of standards and technical collaboration between regulatory authorities can pool expertise to respond to the multifaceted reviews required.

Expanded guidance points

Guidance Point 1: the necessity for HIV prevention trials

There is an urgent need for additional, safe, more effective and more acceptable HIV prevention methods, due to insufficient progress in reducing new HIV infections, absence of a vaccine or a cure and the human, public health, social and economic severity of the HIV epidemic. Developing HIV prevention methods should improve the health and welfare of the communities involved in research and also benefit the wider population at risk of HIV acquisition or transmission. All relevant stakeholders—such as representatives from affected communities, civil society organizations, trial sponsors and researchers, research institutions, industry, public health authorities, regulators, development partners, funding agencies, governments and international organizations—should work together to foster the timely, scientifically sound and ethically responsible development of safe, effective and acceptable HIV prevention methods and improvements to existing ones. Researchers and sponsors—in partnership with the participating community, regulatory and governmental authorities and pharmaceutical manufacturers—must agree on a clear development plan in advance of the conduct of the research that ensures that any trial addresses the pathway and necessary means towards access to a new HIV prevention method.

Urgent need for additional safe, effective and acceptable prevention methods

The availability of PrEP and the anticipated development of other highly effective HIV prevention tools have led to a new era of HIV prevention trials. However, despite the availability of PrEP, new studies into preventive methods are still essential: there were 1.7 million new HIV infections in 2019, while the target for 2030 is for fewer than 200 000 new infections. But the search for new HIV preventive measures is becoming increasingly complex as proven effective methods come to the market. For example, PrEP is highly effective for preventing HIV, but if it is not taken consistently, it is much less effective. This makes access and adherence to PrEP important research considerations. Moreover, trials that test HIV preventive measures have HIV acquisition as an endpoint and hence are most efficient when conducted in populations with a high incidence of HIV infection. High costs of new HIV prevention trials that try to demonstrate efficacy also may be a barrier for the progress of HIV preventive methods. For instance, a comparison trial where trial participants are taking PrEP could become large, long, difficult to interpret and prohibitively expensive. The value of new HIV prevention trials should then be weighed against alternative spending of research resources. The current challenge is to ensure sufficient progress in HIV prevention research in an ethically responsible manner.

Therefore, in order to relieve the enormous public health burden being wrought by HIV, effective treatment continues to be scaled up throughout the world. Mortality due to AIDS-related causes has fallen substantially over the past decade. People taking effective antiviral treatment do not transmit HIV. Nonetheless, there are still more new HIV infections than there are people with HIV who are dying, so the number of people living with HIV continues to rise. Treatment is lifelong, so without more effective primary prevention, the epidemic will not be controlled. This implies an ethical imperative for global support to develop new primary prevention tools and approaches.

Collaborate to foster the timely, scientifically sound and ethically responsible development of HIV prevention methods and improvements

Key stakeholders in HIV prevention research include (among others): representatives from affected communities, civil society organizations, trial sponsors and researchers, research institutions, civil society, industry, public health authorities, regulators, development partners, funding agencies, community representatives, governments and international organizations. They should work together to foster the timely, scientifically sound and ethically responsible development of additional safe and effective HIV prevention methods and improvements to existing ones. Collaboration and networks within HIV prevention research—such as the HIV Prevention Trials Network (HPTN) and the HIV Vaccine Trials Network (HVTN)—are important for many reasons, including ensuring persistence of research efforts, that resources are well-spent, scientific methods are coherent, global priorities are met and that populations are not under-researched or over-researched. Countries that may participate in trials should assess how they can and should take part in HIV prevention product development activities at the national or regional levels, including:

- ▶ Identifying resources.
- ▶ Establishing partnerships.
- ▶ Strengthening their scientific and ethical sectors.
- ▶ Including HIV prevention product research to complement current comprehensive HIV prevention programming.
- ▶ Conducting national information and research literacy campaigns.

Development plan of a pathway towards HIV prevention methods

Product development plans should strive for the broad use of the product across populations at risk and select relevant study populations to advance this aim. In advance of a trial, sponsors and researchers should work with development partners, national governments, local authorities and industry, where relevant, to ensure planning for the manufacturing, regulatory approval, fair distribution and efficient delivery of the HIV prevention method in the community and country engaged in the trial. This plan should also address the potential complexity of the pathway to manufacturing, market access and implementation after early proof of concept.

Funding the pathway

Given the severity of the HIV epidemic, national and international partners must ensure sufficient incentives to foster the development of safe and effective HIV prevention products, and to ensure that they are produced and readily and affordably available to participating communities and countries where a product is tested. This should be done through both financial rewards in the marketplace and through public subsidies.

Guidance Point 2: community partnership

Research teams and trial sponsors must partner with key stakeholders—including key populations, potential participants and their communities, and researchers—from settings and populations where trials are taking place or are planned. These partnerships must be formed in a transparent and meaningful participatory process of trial design, implementation and follow-up that involves all stakeholders as equal partners. Key stakeholders and communities should be involved from the outset in the design, development, implementation and dissemination of results of HIV prevention trials. Researchers and trial sponsors must invest sufficient resources to enable such participation and to ensure good participatory practice.

Importance of forming community partnerships and involving communities

It is essential to form community partnerships and involve communities. Collaborative partnership that engages affected communities at all stages benefits all parties:

- ▶ It increases trust and equity between the participating community and the researchers.
- ▶ It ensures that the trial product and trial methodology meet the needs of those who stand to benefit, minimizes the risk of harm, ensures the methodologies are culturally acceptable and understood, and increases the chance of a clear study outcome.
- ▶ It helps to find solutions to unexpected issues that may emerge before and during the trial and help to explain unexpected trial findings
- ▶ It helps ensure smooth trial functioning.
- ▶ It builds community capacity to understand and inform the research process and raise concerns.

Furthermore, active community participation should strengthen not only local ownership of the research, but also the negotiating power of communities, the research skills of investigators, community leaders and community members, and the social leverage that can be useful in areas of society that are beyond the research trial site. Achieving meaningful participation requires acknowledging structural power imbalances between certain communities and researchers and/or research sponsors, and striving to overcome them. In practical terms, this means establishing outreach and engagement mechanisms to support engagement. Special attention should be paid to empowering women, adolescents, people with comorbidities or living with disabilities and key and other populations that are often excluded from research participation or product access so they may be involved more actively throughout the research process.

Partnership with members of the community will improve the design and conduct of the trial through a co-creation process that may include:

- ▶ Understanding of the cultural norms and practices of the participating community.
- ▶ Understanding of the health beliefs of the study population.
- ▶ Helping to understand or dispel myths that might arise about the product or the trial.
- ▶ Appreciation of the research understanding of the study population.

- ▶ Information for the community-at-large about the proposed research.
- ▶ Input into the design of the protocol and risk reduction interventions.
- ▶ Input into the design of an effective recruitment and informed consent process.
- ▶ Identification of potential social, psychological or other harms that may arise from the research.
- ▶ Insights into the progress of the study and assistance in understanding and overcoming unexpected challenges or barriers
- ▶ Insight into effective methods for disseminating information about the trial and its outcomes.

Involvement from the outset

It is very important that communities that will participate in the trial are engaged in consultations from the beginning of the research concept. This should be an open, iterative and collaborative process that involves a wide variety of participants and takes place under public scrutiny. Failure to properly and genuinely engage communities in the early stages of research planning may result in an inability to conduct and complete important trials. Communities of people affected by research should play an active and informed role in all aspects of research planning, conduct and results dissemination.

Equal partnership

In equal partnerships, there is a shared understanding that the voices of all partners are equally important and essential, and that differences in approaches, expertise and preferences are to be respected. The nature of community involvement should be one of continuous mutual education and respect, partnership and consensus-building around all aspects of the testing of potential HIV prevention products. A continuing forum should be established for communication and problem-solving on all aspects of the HIV prevention product development programme, from Phase I through Phase III, and beyond to the distribution of a safe and effective HIV prevention tool (see Guidance Point 4). All participating parties should define the nature of this ongoing relationship. It should include appropriate representation from participating communities on committees charged with the review, approval and monitoring of an HIV prevention trial. As for investigators and sponsors, communities should also assume appropriate responsibility to assure the successful completion of the trial and the product development programme.

Equal partnership also enhances equity in eligibility criteria for participation; decisions about the level of care and treatment and its duration; and plans for releasing results and distributing safe and efficacious HIV prevention products.

Invest sufficient resources

Researchers and sponsors should allocate sufficient means to enable participation and good participatory practice.¹ This includes providing the funding, time and energy to allow for true collaboration. The expertise of researchers includes research concepts—such as double blind and cause and effect designs—while the expertise of communities

¹ For more information, see the 2011 *Good participatory practice: guidelines for biomedical HIV prevention trials* from UNAIDS.

includes understanding concerns and context, language and communication. This underscores the need for joint literacy, whereby researchers and community groups become sufficiently fluent in the requisite concepts and language to work together productively. Research literacy programmes that include ethics training for study staff can facilitate and enhance cooperation with civil society groups.

Defining and engaging the community

Defining the relevant communities and community representatives for consultation and partnership is a complex and evolving process that should be discussed with relevant local authorities. As more groups and people define themselves as part of the community of interest, the concept needs to be broadened to civil society in order to include advocates, media, human rights organizations, national institutions and governments, and researchers and community representatives of the trial site. Partnership agreements should be in appropriate languages, include a clear delineation of roles for all stakeholders, and they should specify the responsibilities of sponsors, governments, the participating community, advocacy organizations, media, and researchers and research staff. They should be signed by all partners.

Appropriate community representatives should be determined through a process of broad consultation. An agreement should be reached among stakeholders about the definition of the “community” that will be involved in the study and the ways that it can be represented effectively in decision-making early in the design of the study protocol. The process for determining who will be credible and legitimate community representatives should be addressed through a preliminary consultative process between researchers and key members of the community in which the research is proposed to take place. Members of the community who may contribute to the development of a safe and effective HIV prevention product include the following:

- ▶ Representatives of the research population who are eligible to serve as research participants.
- ▶ Other members of the community who would be among the intended beneficiaries of the developed product.
- ▶ Relevant nongovernmental and community-based organizations.
- ▶ People living with HIV.
- ▶ Community leaders – political, traditional and religious.
- ▶ Public health officials.
- ▶ Those who provide health care and other services to people living with and affected by HIV.

Formal community meetings need to be organized in a way that facilitates the active participation of those most affected by the research being proposed, keeping in mind that many communities may be facing stigma and discrimination, harassment, violence or even the complete denial of their existence. The principal investigator and site research staff should work with representatives of affected communities to identify needs related to their participation, including logistical requirements (such as transportation to the meeting site). Educational materials should be designed in an accessible format, using easy-to-understand language, and they should use the languages likely to be spoken by community members.

Adequate consultation and full participation in the planning process will require more than formal community meetings, as such meetings may alienate some people or be inaccessible to others due to timing or format. The principal investigator and site research staff should make efforts to reach out to affected communities, particularly those likely to be excluded from formal settings, through meetings at community centres, workplaces and other frequented locations. In both formal and informal consultations, the timing and length of the meetings should be convenient for community members, using approaches that facilitate two-way communication with two goals in mind: (1) to identify and understand community concerns and needs, as well as the community member's knowledge and experience; and (2) to describe clearly the research being proposed, the related benefits and risks, and other practical implications. Engagement activities should be responsive to context and dynamic over time. Engagement activities should be monitored to assess if activities are achieving important goals.

Guidance Point 3: scientific and ethics conduct and review

HIV prevention trials in all phases and all geographic locations should be conducted only if adequate scientific and clinical capacity and ethics safeguards can be ensured in the setting where the research is to be carried out. The safeguards must include independent and competent scientific and ethics review. In settings where capacity for scientific and ethics review and conduct is limited, relevant stakeholders should collaborate to strengthen and build capacity for scientific and ethics conduct and review oversight processes. Proposed HIV prevention trial protocols should be reviewed by scientific and ethics review committees that are located in, and include membership from, the countries in which the research will be conducted and in which the principal researchers are based. For HIV prevention trials that involve multiple countries or trial sites, the research collaboration should endeavour to build equal partnerships, allowing for optimal use of resources and knowledge, capacity-strengthening and the highest standards of research integrity.

Scientific and clinical capacity

HIV prevention research should only be undertaken in settings and communities where there is adequate scientific and clinical capacity. Disparities in economic wealth, scientific experience and technical capacity between countries and communities may contribute to a situation where the capacity to design and conduct research is lacking or underdeveloped. Building capacity to reduce these disparities could involve the following:

- ▶ Scientific exchange and knowledge and skills transfer between sponsors, researchers, communities and their counterparts, and the countries and communities in which the research takes place.
- ▶ Support around things like information, education and consensus-building in HIV prevention trials for communities from which participants are drawn.
- ▶ Development of laboratory capacity that can support health-care provision and research.

Accordingly, researchers and sponsors should collaborate with countries and communities to determine how site capacity can be sustained after the trial and how research staff expertise can be retained. Site development may build capacity for a specific trial or enhance the ability of a site to compete more broadly for a range of trials. Given the long time frames of HIV prevention research, special attention must be paid to regular updates, communication and transparency in order to build and maintain trust with participating communities, and to sustain site capacity, even after the end of a trial.

Capacity for scientific and ethics review

Scientific and ethics review is typically performed by scientific review and research ethics committees, although some research ethics committees combine scientific and ethics review. Some countries may not currently have the capacity to conduct independent, competent and meaningful scientific and ethics review. If the country's capacity for scientific and ethics review is judged to be inadequate, the sponsor should

be responsible for ensuring that adequate structures for scientific and ethics review are developed prior to the start of research in the country in which the sponsor would like the trial to take place. If that is not or cannot be done, then the research should not take place there. Care should be taken to minimize the potential for conflicts of interest while also providing assistance in capacity-building for scientific and ethics review.

Independent and competent scientific and ethics review

Proposed HIV prevention trial protocols should be reviewed by scientific and ethics review committees that are located in, and include membership from, the country and the communities in which the research will be conducted and in which the principal researchers are based. Trials should be registered with an international trial registry prior to committee review as a condition of approval. Community representatives also must be involved in review of the trial protocol to ensure that the research is culturally appropriate and informed by the concerns and priorities of the community in which the study is to take place. This process ensures that the proposed research is analysed in scientific and ethical terms by individuals who are familiar with the conditions prevailing in the potential research population. Independent ethics review of research protocols ensures public accountability and minimizes concerns about conflicts of interest among researchers occurring due to relationships with the sponsors or pressures from those promoting the research. The scientific and ethics review should involve individuals with adequate expertise and training in science, statistics, ethics and law.

Issues to take into account in the review process

Scientific and ethics review prior to the approval of a trial protocol should take into consideration the following issues:

- ▶ Value and validity of the research protocol.
- ▶ Community participation and involvement.
- ▶ Favourable risk–benefit ratio.
- ▶ Recruitment strategies and methods.
- ▶ Inclusion and exclusion criteria and screening of participants.
- ▶ Informed consent procedures and written information sheets.
- ▶ Access to the requisite levels of prevention, care and treatment for participants and those in the community.
- ▶ Respect for potential and enrolled trial participants and protection of the rights of participants.
- ▶ Confidentiality, privacy and data protection measures.
- ▶ Prevention of stigma and discrimination.
- ▶ Sensitivity to gender, age, race, ethnicity, religion, and relevant societal characteristics.
- ▶ Procedures for ethics monitoring of participants.
- ▶ Quality assurance and safety control.

- ▶ Assessment of potential risks to implementation of the study and proposed mitigation strategies.
- ▶ Plans for post-trial distribution, benefit sharing and dissemination of results.

Guidance and support for capacity-building

Researchers and sponsors need other stakeholders to enable capacity-building. In countries with a heavy disease burden, national governments should assist researchers and sponsors to build capacity. Capacity-building in scientific and ethical review should also be developed in collaboration with international agencies, organizations within the host country and other relevant parties. Researchers and sponsors may collaborate with international nongovernmental organizations that are dedicated to making such improvements.

Equal partnerships in multicountry and multistakeholder research

Real or perceived disparities between sponsors and researchers from different countries and communities should be resolved in a way that ensures equality in decision-making and action. The desired relationship is one of equals, whose common aim is to develop a long-term partnership through South–South and North–South collaboration that sustains site research capacity.

Resources

Development partners, international agencies and governments should make early and sustained commitments to allocate sufficient funds to make HIV preventive interventions a reality. Finding resources includes: (a) funds to strengthen ethical and scientific capacity in countries where multiple trials will have to be conducted; (b) to enhance South–South and North–South capacity-building and technology transfer; and (c) to purchase and distribute future HIV prevention tools.

Starting research while strengthening capacity

Conducting research can also be used as an opportunity to strengthen capacity for scientific and ethics review in the preparatory work for the trial. In some settings, recognized regional bodies may be able to support and reinforce local ethics review processes. It is most important to first strengthen local capacity for ensuring adequate ethical safeguards, whereas local scientific and regulatory capacity can be strengthened by recognized external bodies until the country builds up its own capacity for review.

Guidance Point 4: scientific validity

All HIV prevention research must be scientifically valid. The methodology employed to define and answer the question should be rigorous. In order to ensure scientifically valid results, researchers must clearly articulate in the protocol the products to be tested, the results of previous animal and human testing phases (if relevant), justification of the trial design, justification for any placebo, choice of control and experimental arms, trial endpoints and methodology for statistical analyses. The research question, trial design and statistical analyses should represent current best practices, conform to relevant regulatory standards and be of relevance to local research settings and communities.

Validity

All HIV prevention research—whether it is lab, observational or intervention research—should be scientifically valid. The study should be rigorously designed in order to answer the research question. Research that is not scientifically valid is not ethically justifiable since it carries the risk of potential harms and burdens to participants for little social value—and because it wastes finite research resources.

Trial phases

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

Clinical trial researchers have been designing trials that fall somewhere between Phase II (expanded safety and immunogenicity) and Phase III (large scale trials to assess efficacy). These are called Phase IIB trials, or proof of concept trials. Phase IIB trials may provide an indication of an experimental candidate's efficacy, but they are less costly in terms of money and time, and they require fewer trial participants. However, Phase IIB trials are not generally designed to provide enough information by the end of the trial for regulatory approval of an HIV prevention product; instead, these trials test the general concept of the candidate product and efficiently filter out products that lack efficacy. A Phase III trial would usually have to be conducted to develop a useable and licensable HIV product.

There may be situations where—following discussion between the research partners, community and country authorities—Phase I and II trials are conducted in populations in low- and middle-income countries that are vulnerable to risk and exploitation. For instance, this could occur where an experimental HIV vaccine is directed primarily toward a viral strain that does not exist in the trial sponsor's country but that does exist in the country in which it is proposed that the trial be conducted. Conducting Phase I or II trials in the country where the strain exists may be the only way to determine whether safety and immunogenicity are acceptable in that particular population prior to conducting a Phase III trial. Another example might be a country that decides that—

due to the high level of HIV risk to its population and the level of HIV prevalence in the country—it is willing to test an HIV prevention product concept that has not or is not being tested in another country. Such a decision may result in obvious benefits to the country in question if an effective product is eventually found. The final decision rests with countries. If Phase I or Phase II trials are conducted in the country intending to participate in an eventual Phase III trial, this may assist in building capacity for Phase III trial conduct if Phases I and II are satisfactory. This includes increasing levels of research literacy in the population.

Use of a placebo product

Randomized, double-blind and placebo-controlled trials remain the most accepted way to remove biases and maximize the validity of the trial result. However, a conventional placebo-controlled trial—where the control group only receives a placebo and no further preventive method is provided—is never ethically acceptable for HIV prevention trials. The use of a placebo product in trials can be ethically acceptable in appropriately designed protocols where it is added to the WHO-recommended standard of prevention, as set out in Guidance Point 11.

Best practices for the research question, trial design and statistical analyses

Researchers and sponsors must adhere to best practices for developing the research question, the trial design and for performing statistical analysis. In general, well-established methodology for these aspects has to be followed. In addition, as has been set out in Guidance Point 2, it is important to involve people from communities and settings in which the trials take place to ensure that the research question addresses a health need or priority of those who are the intended beneficiaries. Furthermore, as described in the introduction to this guidance document there is a need for designs that meet the challenge of timely development of new HIV prevention products, while adhering to the requirement of scientific validity.

Establishing an HIV prevention product development programme in countries or communities vulnerable to harm or exploitation

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

- ▶ The product is a vaccine that is anticipated to be effective against a strain of HIV that is an important public health problem in the country.
- ▶ The country and the community either have—or, with assistance, can develop or be provided with—adequate scientific and ethical capability and administrative and health infrastructure for the successful conduct of the proposed research.
- ▶ Community members, policy-makers, ethicists and investigators in the country have determined that their residents will be protected adequately from harm and exploitation, and that the HIV prevention product development programme provides access to the product in a timely manner if it proves safe and effective (see Guidance Point 14).
- ▶ All other conditions for ethical justification (as set forth in this document) are satisfied.

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

Guidance Point 5: fair and inclusive selection of study populations

The selection of study populations and communities from which participants will be recruited must be fair and scientifically justified and transparent. Protocols must have a recruitment plan with relevant information about the proposed study populations to be recruited and who the end users of the intervention are likely to be. Interventions should be tested in the populations likely to use them. In addition, product development plans should strive for broad use across populations at risk. Researchers, trial sponsors and research ethics committees must not arbitrarily exclude persons and populations on the basis of characteristics such as age (including children and adolescents), race or ethnicity, pregnancy, lactation or child-bearing potential, involvement in sex work, substance use, sexual orientation, disability, incarceration, gender identity or coinfections and comorbidities. Such arbitrary exclusion can result in trial results being less impactful as they exclude the people who would most benefit from them or exacerbate health disparities and may impact on the roll-out of effective products to at risk individuals and groups.

Fair and scientifically justified selection

The selection and recruitment of communities and people for participation in a trial must be fair, and they should create a research climate that shows respect for all people. Fair and scientifically justified inclusion encompasses equitable selection of study populations through transparent decisions about who will be included. This is accomplished through the formulation of inclusion and exclusion criteria, and through the strategy adopted for recruiting participants. The scientific goals of the study should be the primary basis for determining which individuals will be recruited and enrolled. Individuals should not be excluded from the opportunity to participate without a good scientific reason. The selection of the research population should be based on the fact that its characteristics are relevant to the scientific issues raised, and where there is a reasonable likelihood that proposed interventions will differ in effectiveness or in adverse events compared to what is known from previous studies.

Recruitment plan in protocol

The research protocol should do the following:

- ▶ Justify the selection and size of the research population from a scientific point of view.
- ▶ Describe how the candidate HIV prevention intervention being tested is expected to be beneficial to the population in which it will occur.
- ▶ Establish safeguards for the protection of research participants from potential harm arising from the research (see Guidance Point 7).
- ▶ Be sensitive to issues of privacy and confidentiality in recruitment procedures (see Guidance Point 10).

Avoiding arbitrary exclusion

Some products are designed and developed for particular groups or routes of transmission. As such, some research protocols may need to exclude individuals and groups for safety reasons on the basis of anticipated biological interactions—such

as with concomitant medicines, sex-related differences in metabolism and potential toxicities—or because of anticipated harms. However, arbitrary exclusion of individuals and populations on the basis of characteristics must be avoided. This includes age (including children and adolescents), race/ethnicity, pregnancy, lactation or child-bearing potential, involvement in sex work, substance use, sexual orientation, sex at birth, gender identity, disabilities or coinfections and comorbidities. Since these populations have often been excluded in the past, a fair roll-out of effective products to affected populations has been difficult because of a lack of data. Researchers and sponsors need to ensure that adequate protections are in place to protect the human rights, dignity, safety and welfare of these individuals and populations.

Towards an equitable evidence base for underrepresented populations

The interests of underrepresented populations should be integrated in developing HIV prevention methods, striving towards a more equitable evidence base for underrepresented groups. Forming long-term partnerships and networks may promote the interests of these groups (see Guidance Point 1).

Gender diversity

Researchers, sponsors and research ethics committees must recognize gender diversity in participating communities and interactions, and pay adequate attention to the distinct needs and contexts of individuals of all gender identities and expressions. Researchers and sponsors should include gender-diverse groups in trials in order to establish the safety, efficacy and/or effectiveness of interventions for these groups.

Women and gender-diverse persons who may become pregnant, are pregnant or are lactating

Women and gender-diverse persons at all points in their respective lifespans—including those who are sexually active and may become pregnant, are pregnant or are lactating—should be recipients of safe and effective HIV prevention products as they are developed. Therefore they should be eligible for enrolment in HIV prevention trials, both as a matter of equity and because in many communities throughout the world, women and gender-diverse persons are at higher risk of HIV exposure, particularly when they are young. Furthermore, pregnancy carries increased risk of HIV acquisition, which is attributable to social risks (e.g., challenges in negotiating condom use) and biological changes in pregnancy.

The most notable data gap in the evaluation of some prevention methods, particularly in Phase I and II trials, is the adequate evaluation of safety and efficacy of HIV prevention products among women and gender-diverse persons, especially during pregnancy. Barriers to the participation of these groups in trials have included imposed contraceptive requirements, issues related to current or future fertility, concerns about safety for the fetus or infant, and fear of being labelled as being at higher risk for HIV exposure.

Also, gender norms and unequal power relations create particular issues with regard to recruitment and informed consent. In some cultures, women and gender-

diverse persons may have constraints on their ability to exercise autonomy; this is also the case with the emerging autonomy of adolescents, particularly in the light of the power and influence of their parents or sexual partners. This inequality may be institutionalized in law and policy. In other cultures, young people may be more informed than their parents, and their view on their participation may differ from that of their parents or partners.

Furthermore, the need for HIV testing or pregnancy testing to assess an individual's eligibility for inclusion in a trial may raise difficult issues regarding the maintenance of appropriate confidentiality. Researchers and research staff should improve recruitment strategies by anticipating and finding solutions to address and overcome these barriers.

The woman or gender-diverse person who is pregnant or lactating should be duly informed about any potential for teratogenesis and other known or unknown risks to the fetus and/or the breastfed or chestfed infant. If there are risks related to breastfeeding or chestfeeding, the woman or gender-diverse person should be informed of the level of risk and the availability of donated or other infant milk substitutes and supportive services, should they wish to make use of them. At the same time, the use of infant feeding formulae can pose risks when there is no clean water.

The decision to participate in an HIV prevention trial should be made by the pregnant or lactating woman or gender-diverse person alone. While the pregnant or lactating woman or gender-diverse person should be provided the opportunity to consult with whomever they wish, no other individual should be permitted to override their decision.

Researchers should observe and study the positive and adverse effects on the children of these women or gender-diverse persons. Research teams should contribute to pregnancy registries, including any registries that may already exist. They should document the outcomes of all pregnancies occurring in the trial to collect data on outcomes of pregnancies that inadvertently occur during the trial, they should follow up with babies born to women and gender-diverse participants, and they should take due measures to prevent mother-to-child transmission of HIV, viral hepatitis and syphilis.

If the safety of the HIV prevention product has not been established for a pregnant woman or gender-diverse person and their foetus prior to commencement of the trial, women or gender-diverse persons who become pregnant in the course of the trial might be discontinued from using the product. This would result in their loss to follow-up. As a result, the question of whether a pregnancy-specific pharmacokinetic (PK) study for pregnant women or gender-diverse persons should be conducted at the stage when a candidate has sufficient promise to advance into a Phase 2b or Phase 3 efficacy trial in adults should be discussed and resolved early in the planning of the research design. In any event, researchers should follow up with women and gender-diverse persons who become pregnant during the course of a trial, including monitoring adverse events, in order to determine a potential relation to the HIV preventive intervention. Any associations identified should be contextualized against baseline rates of adverse pregnancy outcomes (especially including miscarriage and birth defects).

Adolescents

Adolescents should be eligible for enrolment in HIV preventive intervention trials, both as a matter of equity and because children face different risks than adults in many communities throughout the world. Many adolescents are at high risk of HIV infection through sexual activity or injection drug use due to lack of access to HIV prevention education and means. The use of bridging studies designed for safety (and immunogenicity testing for example in the case of an HIV vaccine) that do not include HIV infection as a primary endpoint could be considered as an alternative for younger adolescents, to be carried out in parallel with Phase III trials in adults.

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

People who inject or use drugs

As with other key populations at higher risk of HIV acquisition, people who inject or use drugs should be included and meaningfully engaged in HIV prevention trials (see Guidance Point 2). This will ensure that novel prevention methods are proven to be safe, efficacious and accessible for them, both as a matter of equity and as an expression of their right to health. Researchers and sponsors should also take the necessary steps to safeguard the human rights, safety and welfare of participants.

People who inject drugs are at higher risk of acquiring blood-borne HIV infection, primarily because legal, financial and logistical barriers impede safer use and access to sterile injecting equipment, such as needles, syringes and cookers. They also are at increased risk of acquiring and transmitting HIV through higher risk sexual practices, including because of the risk of sexual transmission in combination with drug use.

Minimizing risks for people who inject or use drugs

Minimizing risks to people who inject or use drugs is done in part by providing appropriate counselling and facilitating access to proven, state-of-the-art risk reduction methods. However, legal barriers, punitive law enforcement practices, logistical challenges and discrimination often prevent people who inject drugs from accessing such harm reduction services, including those comprising the comprehensive package of core interventions for people who inject drugs developed by WHO, the United Nations Office on Drugs and Crime (UNODC) and UNAIDS.² In addition to the provision of condoms, counselling and access to educational information on safe injection practices, key harm reduction services for people who inject drugs include the use of sterile injecting equipment through needle-syringe programmes, opioid substitution therapy (where appropriate), and overdose prevention.³ Where there are insurmountable barriers to ensuring access to WHO-recommended harm reduction for

² For more information, see: WHO, UNODC, UNAIDS. Technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users. Geneva: WHO; 2009

³ Other terms may be used in place of opioid substitution therapy, such as medication-assisted treatment and opioid agonist therapy.

people who inject drugs (sterile injecting equipment and opioid substitution therapy), participating in a trial would provide ethical problems, so HIV prevention trials among people who inject drugs should not proceed.

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

In some settings, people who inject or use drugs may not be seen as priority recipients for limited HIV prevention, care and treatment resources. In the context of research, they may acquire HIV infection during the trial or may be screened out as ineligible when they are found to be HIV-positive. However, the ethical principle of justice requires that both researchers and sponsors work to ensure that access to care and treatment is available to people who inject or use drugs as equitably as it is to others in the community. They should also ensure that the standard of care and treatment is equivalent across high-, low- and middle-income countries (see Guidance Point 12). Care for people who inject or use drugs also may involve the treatment of coinfections and comorbidities, ready access to overdose management, and referral and appropriate linkages to social support networks. A transparent and inclusive process to determine logistics and assign responsibilities for providing this package of care should take place before any trial begins.

In many settings around the world, the consequences of being identified as a person who injects or uses drugs are extremely serious. Precautions should be taken to ensure that recruitment and retention are voluntary, and that the rights of participants to confidentiality and privacy are not breached (see Guidance Point 13). Recruitment within voluntary drug treatment centres—especially by service providers, upon whom people who inject drugs are dependent for their ongoing care—may pose special problems around voluntary trial participation. Generally, potential trial participants should not be recruited by their service providers, and where respondent-driven recruitment and other snowball-type recruitment techniques are used, confidentiality should be emphasized to recruiters. Research teams should be trained to identify when a potential participant is unable to make a voluntary, informed decision about trial participation, but being under the influence may not be sufficient reason to assume a lack of capacity to decide. Participants should be clearly informed of any limits to confidentiality that researchers must follow due to national or local regulations.

It is not uncommon for people who inject or use drugs to be incarcerated because of their drug use or for peripheral reasons, such as sex work or because they are targeted under loitering and vagrancy laws. Researchers should anticipate that some trial participants could be incarcerated during the course of the trial, and they should develop an incarceration protocol describing the conditions to be followed to ensure that ongoing ethical trial participation is preserved. The incarceration protocol should reflect and use the specific protections that appear in the relevant regulations related

to research with those who are in jail or imprisoned. This should include an option and procedures for the participant's voluntary withdrawal from the trial. The protocol should address:

- ▶ Confidentiality and voluntariness.
- ▶ Access to risk reduction measures and a physician while incarcerated.
- ▶ Post-release planning, including for consent to re-join the trial.

In particular, mechanisms should be put in place to ensure that there is no interruption of antiretroviral therapy or opioid substitution therapy. All relevant stakeholders, including prison authorities, should agree to these provisions in advance of a trial.

Assuming that participants who inject drugs should be provided only with vouchers or in-kind compensation—rather than cash reimbursement equivalent to what is provided in trials involving other populations—is discriminatory. Participants who inject drugs should be reimbursed in the same way as other participants.

Guidance Point 6: social and political contexts of vulnerability

The people who could significantly benefit from new, safe and effective HIV prevention interventions often live in social or political contexts of vulnerability to exploitation, prosecution or other harms. Researchers, trial sponsors and research ethics committees should be mindful of people and populations living in these contexts when establishing the safety, efficacy and effectiveness of interventions, and when maximizing the benefits of future successful HIV prevention options specifically for the people and populations that can most benefit from them. Researchers and trial sponsors should work with communities and relevant civil society stakeholders to overcome legal, ethical, regulatory and other challenges to the research participation of populations living in these contexts. Researchers and trial sponsors should take measures to protect the safety, dignity, human rights and welfare of participants, and to prevent discrimination or prejudice. Researchers and trial sponsors must recognize that participation in research may also increase the risk of social, psychological or legal harms for participants, including through inadvertent disclosure of information, stigmatization and discrimination and take adequate measures to prevent and/or mitigate such harms.

Social and political contexts of vulnerability

In order to test if an HIV prevention intervention works, large numbers of individuals at high risk of acquiring HIV must be recruited for clinical trials. However, participating communities and populations may be characterized by multiple social and political contexts of vulnerability, particularly for large-scale efficacy trials. Such social and political contexts include the criminalization of drug use and sex work, homophobia, transphobia, gender inequality, systemic racism, poverty and housing instability. The same factors that put these individuals at increased risk for exposure to HIV also increase their risk of experiencing stigma and discrimination, violence, cultural exclusion, social inequality, economic exploitation, incarceration and political oppression. At the same time, it is precisely these populations who stand to benefit most from the successful development of a new HIV prevention product or method.

Risk of harm

Decision-making around conducting an HIV prevention trial needs to consider the ways that the trial might change contexts so that vulnerabilities are increased or decreased. On the one hand, a trial might increase a participant's risk of exposure to stigma and discrimination if it highlights a population's increased vulnerability to HIV exposure or the participant's membership of a particular population vulnerable to stigma or discrimination, or if it inadvertently discloses personal information. On the other hand, a trial might decrease vulnerability if it empowers the participating community or provides tangible assistance to participants, such as by improving the accessibility, affordability and quality of appropriate health-care services in the participating community. A social, cultural and political analysis should be carried out early in the research planning process to assess determinants of vulnerability in potential participating communities, such as poverty, gender, age, ethnicity, sexuality, health, employment, education and legal conditions. Findings from this analysis should inform a plan to mitigate risks and maximise benefits in the design of research protocols, which should be sensitive throughout the course of a trial to emerging information about benefits or the incidental risks for social harm.

The research protocol should mention which aspects of the social context may lead to increased vulnerability. It should also mention the safeguards implemented and measures taken to prevent and overcome them. In some countries or communities, conditions affecting the potential vulnerability or risk of exploitation of participants may be so severe that the risk outweighs the benefit of conducting the study in that population. In those instances, HIV prevention trials should not be conducted.

Sensitivity to factors of potential vulnerability—including language and cultural barriers—should inform procedures for recruiting and screening potential participants. It should also influence informed consent processes and the support, care and treatment that participants receive related to the trial. If a scientifically appropriate population is identified as living in a context that makes them vulnerable to social harm, specific safeguards should be implemented to protect individual participants and ensure their confidentiality, freedom to decline participation in the study and right to withdraw at any time without penalty.

Reduce challenges to the inclusion of specific populations

Researchers and trial sponsors should work with communities and relevant civil society stakeholders to mitigate legal, ethical, regulatory, language, disability-related and other challenges to the inclusion of specific populations in trials. For example, people who inject drugs may face several layers of vulnerability:

- ▶ Criminalization of drug use through punitive, often harsh, law enforcement practices, including incarceration, can impede recruitment and participation for individuals who inject drugs.
- ▶ Generalized stigma and discrimination, including from some health-care professionals, law enforcement figures and policy-makers.
- ▶ Personal mental health issues, preceding or resulting from their drug use.
- ▶ Coinfections and comorbidities, such as tuberculosis, viral hepatitis and sepsis.
- ▶ Poverty.
- ▶ Racism if they are members of certain racialized groups.
- ▶ Marginalization.

Gender adds an additional layer of vulnerability for people who inject drugs who are women, gay men and other men who have sex with men, transgender or intersex people, and sex workers. They may experience increased vulnerability to unprotected sex and unsafe injections, as well as exploitation, discrimination, lack of sensitivity to their specific needs, the possibility of children being removed, and underresourcing of services to meet their needs.

Prior to commencing a trial, researchers and trial sponsors should conduct formative research to gain understanding of the particular contextual challenges faced by people who inject drugs and to begin building trust with people who inject drugs and their networks. The research protocol should describe the identified contexts of vulnerability and the steps that have been or will be taken to create a safe, enabling environment for trial participants. HIV prevention trials should not be conducted where there are insurmountable barriers to ensuring the safety, protection and confidentiality of trial participants (see Guidance Point 13). For this reason—and because adherence to the principle of autonomy cannot be guaranteed—HIV prevention trials should not be

conducted in compulsory drug detention centres or in prisons unless the research specifically studies a health need and priority for prisoners. If research participants in ongoing studies are incarcerated, special protections for the continued inclusion of these persons are needed.

To protect safety, dignity, human rights and welfare, and to prevent discrimination

Researchers and trial sponsors should take measures to protect the safety, human rights and welfare of participants, and to prevent discrimination or prejudice. For example, they may take professional development courses on stigma in health care and other settings, or on culturally appropriate care and language. Staff in the trial sites should be educated about stigma and discrimination around key populations, gender, human rights and health care, and gender-based violence. Staff should know how to identify participants affected by these issues and be familiar with the resources available or services to refer them to.

Guidance Point 7: potential harms

Researchers must specify as fully as possible in protocols and informed consent documents the nature, magnitude and probability of harms to both participants and others that may result from the intervention and procedures. These harms may include physical harms, discomfort and side-effects, social, economic, legal and psychological impacts. Study protocols and informed consent documents should explicitly specify how potential study-related harms will be managed. The protocol must specify the plans to minimize, mitigate and remedy these potential harms. Potential harms must be appropriately balanced in relation to the anticipated individual and societal benefits of the research.

To specify potential harms to participants and others

Participation in HIV prevention trials may involve physical, social, economic, legal and psychological harms. Harms can be context specific and therefore must be identified in conjunction with participating communities.

Physical harms

Physical injuries may be sustained due to research-related activities, such as blood drawing or other medical interventions. For example, injections may result in pain, occasional skin reactions or possibly other biological adverse events, such as fever and malaise. Furthermore, despite previous safety testing of microbicide products, trial participants and/or sexual partners who are exposed to a product may experience adverse effects, including those that may increase their risk of HIV acquisition. In the case of microbicides containing antiretroviral drugs, there may be systemic absorption of active ingredients, with the possibility of developing antiretroviral resistance should HIV infection be acquired. In trials where the experimental product has antiretroviral properties, including PrEP trials, individuals who acquire HIV infection may develop resistance to the antiretroviral drug in the experimental product. In these cases, the resistance could be passed on to third parties, such as sexual partners, fetuses and infants. Physical harms also might occur indirectly, such as an increase in domestic violence for women who participate in a trial (also see Guidance Point 10).

Vaccine trial participants who are exposed to HIV may have a greater risk of developing established infection—or of progressing more rapidly once infected—than if the vaccine had not been administered. If a vaccine candidate elicits a positive HIV antibody test in the absence of HIV infection—a “false positive” HIV test—negative social consequences may result similar to those that may exist for those actually living with HIV. Protocols and informed consent procedures should also include discussion of the possibility of testing positive for HIV antibodies without being infected with HIV. Laboratory techniques that differentiate between vaccine-induced antibodies and actual HIV infection should be provided at the clinical site, and trial participants should be provided with necessary documentation to demonstrate that their participation in an HIV vaccine trial may be the cause of their HIV antibody seropositivity.

Some HIV prevention interventions may alter the participant’s immune response to HIV acquisition, and thus have the potential for false negative diagnostic results and delayed diagnoses. There are potential impacts of false negative results, including psychological impacts, medical impacts (implications of a delayed diagnosis), and

public health impacts (potential onward transmission, including transmission of resistant virus). Appropriate diagnostic algorithms should be included in studies involving such interventions.

Social, psychological, economic and legal harms

Participation in a complicated and lengthy trial that involves intimate matters, repeated HIV testing and exposure to culturally different scientific and medical concepts may cause anxiety, stress and depression. It also may result in stress between partners in a relationship. Participation, if it becomes publicly known or known to a partner, may also cause stigma and discrimination against the participant if they are perceived to be living with HIV or at higher risk of acquiring HIV infection. This is particularly the case for women, gender-diverse groups, adolescents and already marginalized populations, or if participation identifies a person as belonging to a particular stigmatized group. HIV has been associated with criminalized and stigmatized behaviour, including injection or other drug use, sex work, gender diversity and sexual relations between men, as well as with behaviours that may not be condoned, such as premarital or extra-marital sexual activity. For example, participation in a trial may lead to someone being suspected of injection or other drug use or to a man being “outed” as having same-sex sexual relations. Discrimination can take the form of accusations or abuse, affect marriage prospects and result in social ostracism, job loss, and the denial of property or inheritance rights or health care. Participation in a trial may also lead to altered risk behaviour even when a placebo is used, as there may be an assumption of protection and associated increase in risk behaviour. Social, economic, legal and psychological harms must be identified through preliminary research and in consultation with participating communities (also see Guidance Point 6).

In settings where the identities of study participants are criminalized—or where such participants face social stigma and discrimination—trial sponsors and investigators should prospectively engage with relevant authorities, community leaders and civil society stakeholders to determine if the proposed study can be conducted safely. If it can, they should also determine how the stakeholders engaged can contribute to the safety of study participants. Such engagement should occur on an ongoing basis for the duration of the study in order to reinforce the protection of study participants. Sponsors and investigators also should actively engage with women leaders in different communities to design recruitment and trials in a manner that reduces the risk of gender-based violence and institutes mechanisms for referring victims of violence to the supports and services that they need.

Management of potential harms

Study protocols and informed consent documents should explicitly specify how potential study-related harms will be managed. Study documentation should specify who is responsible for paying upfront costs associated with such management. Management of potential harms should include plans to minimize, mitigate and remedy those harms. This implies that trial sponsors, countries and researchers (among others) should ensure that trials take place only in communities where confidentiality can be maintained (see Guidance Point 10). Trials should also occur in communities where participants will have access to—and can be referred to—ongoing psychosocial services, including counselling during screening and post-enrolment, social support groups, support for victims of violence and legal support (see Guidance Point 12). Risk minimization should include support counselling, rigorous and ongoing

monitoring of potentially harmful consequences of trial participation, including trial-related stigma and discrimination. If a participant acquires HIV during a trial where the experimental product has antiretroviral properties, then the research team must ensure that resistance testing is performed to identify the antiretroviral medicines to be used in treatment.

Treatment and compensation for injuries

The potential for adverse reactions to a candidate HIV prevention product—as well as possible injuries related to the conduct of HIV prevention research—should be described, as far as possible, in the research protocol and fully explained in the informed consent process. Both the protocol and the informed consent process should describe the nature of medical treatment to be provided for injuries and how participants can get access to it, as well as compensation for harm incurred due to research-related activities and the process by which it will be decided whether an injury will be compensated. HIV infection acquired during participation in an HIV prevention trial should not be considered a compensable injury unless directly attributable to the prevention product itself being tested, or to direct contamination through a research-related activity. In addition to compensation for trial-related biological and medical injuries, appropriate consideration should be given to compensation for social or economic harms. Consideration should be given to appointing an ombudsperson who can intervene with outside parties on behalf of participants, if necessary and requested.

A reasonable risk-benefit balance

Scientific and ethics review committees must be satisfied that the potential harms to individual subjects are minimized, and that the potential benefits to individual participants, the participating community and society in general are reasonable, proportionate and outweigh the risks.

Guidance Point 8: benefits

Researchers must provide an accurate statement in protocols and informed consent documents of the anticipated benefits that may result to participants and others from the intervention and procedures. These may include physical, societal, economic, and psychological benefits. The protocol should outline any services, products and other ancillary interventions provided in the course of the research that are likely to benefit participants in the trials, including arrangements to refer for care or other services. Such benefits should not be presented in a manner that unduly influences freedom of choice regarding research participation.

Defining the level of benefits

Participation in a trial may also bring a range of benefits to participants and their wider communities. If the new tool under investigation is effective, some people in the experimental arm who would have acquired HIV infection will not do so. All participants may gain physical benefit from regular engagement with the clinicians in the research team and through appropriate management or referral of incidental physical or mental health issues. Ongoing participation in a trial may also bring psychosocial benefits through peer-support and feelings of altruism. The incidence of new HIV infections is often lower in trial participants than had been anticipated from data from the same community before the trial interventions began.

There may also be indirect additional benefits arising from participation in the trial. The partners, family and wider social networks of participants in the trial will benefit from any new HIV infections averted. HIV-negative sexual partners will be directly protected from HIV infection, while wider family and social networks will not have the psychosocial and economic effects that may follow when a person acquires HIV infection.

Societal benefits may follow from greater knowledge about HIV and how to prevent it and, should the intervention prove to be cost-effective, there may be wider economic benefits to the trial community or to the health system. In some settings, the trial may also facilitate greater engagement by policy-makers with HIV prevention in general or with specific aspects that the study highlights.

There should be an ongoing iterative consultative process to facilitate local or national decision-making about the appropriate level of support, care, and treatment provided to potential and enrolled participants. At a minimum, the research team should ensure that participants benefit from access to the standard of prevention (see Guidance point 11), access to care and treatment for HIV (see Guidance Point 12), other benefits of participation, ancillary care and reimbursement for time spent.

Ancillary care and screening procedures

Before interventions are administered, many protocols use a screening procedure. The screening procedure is part of the research study. In this screening process, researchers look for specific conditions or characteristics of a participant that can lead to inclusion or exclusion. During the screening process or other parts of the study, researchers may identify conditions using study procedures such as blood draws or questionnaires, but treatment for these identified conditions is not part of the scientific study. Before participants are enrolled in the research study, researchers and sponsors should inform them how they are transitioned to care and treatment when screened out and whether

the sponsor can provide for the services needed (see Guidance Point 12). Researchers and sponsors should plan in advance for the approach to ancillary care, outline it in the protocol, inform potential participants about the ancillary care and form the necessary partnerships to address such ancillary care. For women and gender-diverse persons who may become pregnant, appropriate reproductive and sexual health counselling and ancillary services—including the offer of family planning services—should be provided to trial participants.

Reimbursement and undue inducement

Participants should be reimbursed for travel and other expenses related to their participation in an HIV prevention trial. In recognizing the time and inconvenience their participation entails, the appropriate form and level of extraneous non-health incentives will depend on the local economic and social context. Although participants may regard reimbursements as personal benefits, it should not form part of the risk–benefit analysis by researchers or research ethics committees. Only anticipated benefits of study-related procedures required for the safe and scientific conduct of the trial should be considered in the risk–benefit analysis: that is, only health-care benefits derived directly from the study design. Extraneous benefits—such as payment or ancillary services, including HIV risk reduction interventions or reproductive health-care services—should not be considered in the risk–benefit analysis. Concerns that any form of care and treatment promised to participants during research on HIV preventive interventions could act as an undue inducement to participation are unwarranted.

Some may argue that ensuring access to WHO-recommended prevention, care and treatment services for participants introduces local inequalities and is therefore unjust when nonparticipants do not receive those same services. However, all scale-up programmes involve temporary inequalities in the participating community until universal access can be attained. Achieving equal justice is a process of gradual realization.

Guidance Point 9: informed consent

Research teams and trial sponsors should ensure that participants provide voluntary informed consent based on adequate, accurate and appropriately conveyed and understood information before enrolment, as laid out in international ethical guidance documents. Specific measures should be taken to support and protect persons who are, or who may be, limited in their ability to participate voluntarily or provide informed consent. Participants have a right to refuse to participate or withdraw at any point in the trial without negative consequences. For trials involving children, the permission of a parent or legal guardian is generally required along with the assent of the child, unless strict requirements for parental waiver can be met. Separate informed consent should be sought for procedures that are beyond the activities described in the protocol, for example data banking and biobanking.

General considerations on informed consent

HIV prevention trials require informed consent for participation. Informed consent is a process, not just a piece of paper to be read and signed. Researchers must give timely, accessible, understandable and adequate information before participants are enrolled. Once participants are enrolled, efforts should then be made throughout the trial to obtain assurance that their participation continues to be on the basis of free consent and adequate understanding of what is happening. Informed consent must be renewed when substantive protocol changes occur or when new information becomes available that may affect willingness to continue participation.

Understanding

Researchers should describe in the protocol how they will assess the understanding of the trial among potential participants before their enrolment to be sure they clearly understand that they are participating in a trial and not in an HIV prevention programme. Researchers also need to continually assess whether participants adequately understand the trial throughout the trial duration.

Screening candidates for eligibility for participation in the trial

Informed consent must be obtained before screening takes place. The screening process involves interviews on personal matters, such as sexual behaviour and drug use, which are protected by a right to privacy. To guarantee this right, confidentiality must be strictly observed and appropriate measures of personal data protection should be put in place (see Guidance Point 10). The screening process may also involve medical tests—such as taking blood samples, tests for HIV, other sexually transmitted diseases, viral hepatitis and pregnancy; examinations of the male and female reproductive systems and a general physical examination—the results of which are also private and should be kept in confidence. Informed consent should be obtained to undergo this screening process, based on a full divulgence of all material information regarding the screening procedures and an outline of the HIV prevention trial in which participants will be invited to enrol if they are found to be eligible. Informed consent should also be given for the HIV test, and if the result is HIV-positive, for linkage to clinical and social support services.

Consent form

The information should be presented in appropriate formats and languages, including a written information sheet and visual aids to facilitate understanding where necessary. There also should be oral communication of information, especially for participants who may be unable to read, or who may be visually impaired and standardized tests for assessing comprehension.

Content

Individuals should be given adequate information about the nature and length of participation in the trial, including the risks and benefits posed by participation. This will ensure they are able to give their informed consent to participate. Time should be allowed to consider participation, discuss with others (such as partners), and ask questions. Candidates also should be informed of their rights as participants, including the right to confidentiality (see Guidance Point 10) and the right to refuse to participate or to withdraw from the study at any time without penalty.

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

- ▶ The reasons they have been chosen as prospective participants, including if this is because they are part of a population at higher risk of HIV exposure.
- ▶ That the HIV prevention product is experimental, and it is not known that it will prevent HIV infection or disease.
- ▶ The phase of the trial and information obtained from previous studies.
- ▶ That some of the participants will receive a placebo instead of the candidate HIV prevention product through random assignment (when applicable).
- ▶ The nature of their access to the standard of prevention (see Guidance Point 11).
- ▶ That some of the trial participants may become infected despite the risk reduction efforts, particularly in the Phase III trials, which feature large numbers of participants at higher risk of HIV exposure.
- ▶ The specific risks for physical, psychological and social harm, the types of treatment and compensation that are available for harm received during the trial, and the services to which they may be referred should harm occur (see Guidance Point 7).
- ▶ The nature and duration of care and treatment that is available—and how it can be accessed—if they become infected with HIV during the course of the trial (see Guidance Point 12).

Inclusion of persons who are limited in their ability to participate voluntarily or provide informed consent

Researchers and research staff should take special measures to protect persons who are, or who may be, limited in their ability to participate voluntarily in an HIV prevention trial due to their social or legal status (see Guidance Point 6). The presumption is that all adults are legally competent to give informed consent to participate in an HIV prevention trial, but voluntary participation may be compromised in some situations by factors, such as social marginalization, political powerlessness

and economic dependence. Voluntary participation also may be compromised in instances where there is a cultural tradition of men holding decision-making authority in marital relationships, parental control of women, and other forms of social subjugation and coercion.

In some communities, it is customary to require the authorization of a third party—such as a community elder or head of a family—in order for investigators to enter the participating community or to approach individuals. In those cases, the third party only gives permission to invite individuals to participate: such authorization or influence must not be used as a substitute for individual informed consent. Trials should not be conducted where truly voluntary participation and ongoing free informed consent cannot be obtained. Authorization by a third party in place of individual informed consent is permissible only in the case of some minors who have not yet attained the legal age of consent to participate in a trial. In cases where it is proposed that minors will be enrolled as research participants, specific and full justification for their enrolment must be given, and they must be supported to understand the information provided and to be able to provide or withhold their own assent or consent in the light of their evolving capacities.

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

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

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

Parental permission and assent

As with all other trials involving adolescents, the permission of a parent or legal guardian is generally required along with the assent of the child. Unless exceptions are permitted by national legislation or national ethics guidance, consent to participate in an HIV preventive intervention trial must be secured from the parent or guardian of an adolescent who is a minor before the enrolment of the adolescent as a participant in the trial. The consent of one parent is generally sufficient, unless national law requires the consent of both. Parental consent for sensitive research can act as a

barrier to enrolment and can cause social harms like parental sanction, and it might skew enrolment for low-risk adolescents. Every effort should be made to obtain the adolescent's informed decision to participate in the trial. Information must be presented in an accessible and acceptable format to ensure informed decision-making, and the adolescent's refusal to participate must be respected.

Separate informed consent for procedures that are beyond the activities described in the protocol, for example data banking and biobanking

Separate informed consent is needed for studies that go beyond what is described and needed in the protocol, such as consent for additional testing, subsequent research, access to data, data transfer, testing or vaccine-induced seropositivity, and genetic testing and cohort biological characteristics. Separate informed consent should be sought at the same time as study consent to ensure that the research outcomes are maximized and that the challenge of reobtaining the consent of participants is avoided. Participants must be aware that they can decline data banking or biobanking without affecting their choice to participate in the main study.

Data banking and biobanking processes should be in line with international and national legal and ethical guidance documents. Participants should be informed about the following:

- ▶ The collection, use and period of storage of biological samples and specimens provided by participants, and the options for their disposal at the conclusion of the trial. This includes the option to refuse to allow the use of such samples or specimens beyond the scope of the specific trial in which individuals have participated.
- ▶ The use, confidentiality, period of storage and disposal of personal data, including genetic information. This includes the option to refuse to allow the use of such data beyond the scope of the specific trial in which individuals have participated (see Guidance Point 13).

Guidance Point 10: confidentiality and privacy

Researchers have an ongoing obligation to participants to develop and implement stringent procedures and systems to maintain the confidentiality and security of personal information, including information collected during a trial and after its completion. Researchers should assess the privacy risks for participants, mitigate these risks as much as possible and describe the remaining risks in the protocol.

To maintain confidentiality and security of information

All study participant data must be kept confidentially whether they are of a sensitive nature or not. A participant's age, address and marital status are equally important to maintain confidential as their sexual preferences and comorbidities. However, the negative consequences of a data breach to a participant of an HIV prevention trial may be far greater due to the sensitivity of information about a study participant that is collected as part of their participation in HIV vaccine and prevention research. Personal information necessary for the study – such as sexual behaviour, drug use, HIV status, medical conditions or even their association with the trial—could be highly stigmatizing and might be socially harmful if people outside the study and not bound by confidentiality discover it, including the police or law enforcement agencies. It is therefore of particular importance in HIV prevention trials that the research team commits to keeping confidential all personal information of potential and enrolled participants in order to minimize the likelihood of such harm. They also must explain to participants what measures will be taken to protect their privacy and personal information, and what limitations may exist to their ability to do so.

All participants are entitled to confidentiality of their personal information disclosed or discovered during the recruitment and informed consent processes, and during conduct of the trial. Community involvement should not compromise the confidentiality of study participants. This is particularly important for participants who live in social contexts of vulnerability and who may be socially susceptible to stigma and discrimination (see Guidance Point 6). There may be specific exceptions to the duty of confidentiality for legal or ethical reasons, but those exceptions should be identified prospectively and disclosed to the participant during the informed consent process.

Partners of people who test positive for HIV during participation in trials must not automatically be informed of their partner's status. WHO recommends voluntary assisted partner notification services where people with HIV can choose a range of approaches to support their partner or partners to be offered HIV testing. Some people may decline and this must be respected. For example, women may decline if they fear adverse reactions or intimate partner violence. Researchers and research staff should be sensitive to the possibility of intimate partner violence as a result of partner notification; both health-care workers and research staff will need explicit training on how to maintain confidentiality in such sensitive situations.

Inadvertent disclosure of a woman's involvement in a trial to her partner may lead to increased exposure to violence or abuse. This could be violence from partners or family members (including acting on a belief that the individual "failed to get permission" from a partner or spouse). The sponsor and researcher should have a plan to prevent and respond to this, and a mechanism for people to come forward to report possible negative consequences (see Guidance Point 8).

Research may involve collecting and storing private and sensitive data relating to individuals and communities, including data derived from biological samples (see Guidance Point 9). Measures of data protection are of major importance in large-scale studies such as HIV prevention trials, which establish large databases to integrate clinical data and monitor public health effect. Decisions regarding which personal data are to be collected and stored must be based on the requirements of the trial design and the medical needs of participants (see Guidance Point 9). Personal, identifiable data should not be stored longer than necessary. Procedures should be in place to monitor the use of the system where the data are stored in order to detect potential or actual security threats. Systematic guidance on data security can be found in *The privacy, confidentiality and security assessment tool (2019)* and *The privacy, confidentiality and security assessment tool: user manual (2019)*, both from UNAIDS (see the Bibliography).

To assess and mitigate privacy risks

Researchers have an ongoing obligation to participants and the host community to develop and implement procedures to protect the privacy of participants. Such procedures might include interviewing participants out of doors or in other locations where they cannot be overheard. To protect privacy, workers in the clinic or programme setting where recruitment is taking place should first ask potential participants whether they would be willing to speak to a researcher who will provide information about trial participation. In the case of adolescents below the legal age of consent being recruited for endpoint efficacy trials, researchers should inquire whether their parents are aware of the adolescent's sexual behaviour and explain that parental permission will be required for enrolment (if that is a legal requirement in the country), unless conditions for a waiver of parental consent can be met. In the case of media interest in the trial, research staff members should also advise participants of possible negative impacts resulting from public exposure. Community advisory boards may need training to enable members to participate in interviews about the trial in ways that do not compromise the duty of confidentiality owed to individual participants or jeopardize their right to privacy.

Guidance Point 11: standard of prevention

Researchers and trial sponsors should, at a minimum, ensure access to the package of prevention methods recommended by the WHO for every participant throughout the trial and follow-up, including during any pre-enrolment or “run-in” period prior to randomization, and in cohort studies set up to establish the feasibility of subsequent prevention trials. A departure from the WHO-recommended standard can be justified only if relevant stakeholders, inclusive of community stakeholders, are meaningfully engaged and accept a compelling scientific or biological rationale for the departure from the standard. Any such departure from the standard should be explicitly approved by the research ethics committee. When new HIV prevention methods are scientifically validated and recommended by WHO, they should be added to the standard of prevention as soon as is practically possible based on consultation among relevant stakeholders, including community stakeholders. The uptake of and adherence to components of the standard prevention package should be monitored actively by the trial team and other stakeholders while the trial is ongoing.

WHO-recommended package of prevention methods

WHO recommends a range of HIV prevention options and provides prevention guidance for a variety of different populations.^{4,5,6,7,8} These recommendations and guidance are developed by an external WHO guidance development group that follows a standard WHO process using Grading of Recommendations, Assessment, Development and Evaluations (GRADE), a transparent framework for developing and presenting summaries of evidence. This process evaluates evidence for methods and interventions and takes into account the values and preferences of end users and providers, as well as equity, costs and feasibility. WHO recommendations and guidance are global, but because the primary audiences are in low-resource settings, considerations of cost and feasibility in those settings is a critical part of the guidance process. WHO considers the prequalification of the medicine or product and its inclusion on the essential medicine list.

⁴ For more information, see: World Health Organization HIV prevention - <https://www.who.int/teams/global-hiv-programme/hiv-prevention/>

⁵ WHO 2014 Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children

⁶ WHO 2015 Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV

⁷ WHO 2016 Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations

⁸ WHO 2020 Preventing HIV through safe voluntary medical male circumcision for adolescent boys and men in generalized HIV epidemics: recommendations and key consideration

The most recent comprehensive guidance on the WHO recommended package of prevention interventions is available on the WHO website⁴. It consists of several essential health sector interventions, tailored to particular populations and epidemic contexts.

WHO recommends that HIV prevention interventions should be ensured together with services to prevent and manage coinfections and comorbidities (including sexually transmitted infections, tuberculosis, viral hepatitis and mental health); that they should address broader sexual and reproductive health and rights needs; and that they should include critical enablers to address structural and legal barriers to access. Access to HIV testing and offer of partner services to support prevention choice is recommended and is essential for some prevention interventions.

As of January 2021, key elements of this package in relation to this guidance document include:

Sexual transmission:

1. Male and female condoms and lubricants in all settings.
2. Post-exposure prophylaxis (PEP) in all settings.
3. Pre-exposure prophylaxis (PrEP) for people at substantial HIV risk.
4. Voluntary medical male circumcision for HIV prevention for adolescent boys and men in high HIV burden settings in eastern and southern Africa.
5. Treatment of other sexually transmitted infections in all settings.

Parenteral transmission

1. Harm reduction for people who inject drugs in all settings.
 2. PEP in all settings.
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Protocols for HIV prevention research obligate researchers and trial sponsors to ensure access to the full WHO-recommended package of prevention. Access to that package should be provided throughout all trial phases: for example, during pre-enrolment, the run-in period or in cohort studies that precede intervention trials. The standard of prevention should be defined in the study protocol and in informed consent documents. Researchers should monitor the uptake of prevention modalities by participants (see Guidance Point 13).

Departure from the standard of prevention

In some circumstances, there may be a lag between WHO recommending a new product and it being manufactured commercially. In these situations, it may not be possible to include this new product in the standard of prevention until manufacturing capacity has been established and product is available.

A departure from the WHO-recommended standard can be justified only if relevant stakeholders, inclusive of community stakeholders, are meaningfully engaged and accept a compelling scientific, biological or manufacturing rationale for the departure from the recommended standard. Any departure from the standard should be explicitly approved by the research ethics committee (see Guidance Point 3). An example of a compelling scientific or biological rationale is when the mechanism of action of the intervention is the same as a known effective prevention,⁹ or when using the intervention in combination with a WHO-recommended prevention method leads to unacceptable research risks for the participants, such as when the dosage would become too high.¹⁰ Another example of a potentially justifiable departure is to withhold the WHO-recommended standard of prevention from those who voluntarily and knowingly refuse this standard or who fail to use the WHO-recommended standard for clinical reasons.¹¹

The uptake of components of the standard prevention package should be monitored actively by the trial team and other stakeholders while the trial is ongoing (see also Guidance Point 13).

⁹ For example, the HPTN 083 [NCT04692077] and HPTN 084 [NCT04692077] studies provided either systemic cabotegravir or systemic tenofovir disoproxil fumarate and emtricitabine to all participants.

¹⁰ For example, participants receiving implants of tenofovir alafenamide could not also take oral tablets containing tenofovir disoproxil fumarate. [Simpson SM, Widanapathirana L, Su JT, et al. Design of a Drug-Eluting Subcutaneous Implant of the Antiretroviral Tenofovir Alafenamide Fumarate. *Pharm Res.* 2020;37(4):83]

¹¹ For example, the Mosaico vaccine trial recruits only participants who choose not to take oral PrEP. [NCT03964415]

Guidance Point 12: care and treatment

Researchers and sponsors should ensure linkage to treatment programmes in line with WHO guidance for optimal treatment for all participants who test positive for HIV infection during screening or who acquire HIV during the trial. Plans for access to the optimal national standard of HIV-related care and treatment must be explicit in the protocol and should include drug resistance testing.

Level of care and treatment

Sponsors need to ensure linkages to national treatment programmes that are in line with WHO guidance for optimal treatment for participants who test positive for HIV infection during screening or who acquire HIV during the course of the trial.¹² This includes antiretroviral therapy and related care and support. Treatment services in line with WHO recommendations should be delivered through national programmes.

While a trial may aim to study an HIV prevention intervention or technology, incident HIV infection is the endpoint for most trials. Care and treatment for HIV infection are therefore not ancillary since the researchers and sponsors already know in advance of the trial that HIV acquisition may occur. The access to antiretroviral treatment for trial participants who acquire HIV during the trial requires planning for logistics and implementation.

Prior to the trial, researchers and trial sponsors should collaborate with governments and communities in low-income settings to explore, develop and strengthen national and local capacity to deliver the highest possible quality of HIV prevention, care and treatment services through strategic investment and development of trial-related resources. In most situations, no single stakeholder should bear the entire burden of providing resources for such services, and the central responsibility for delivery should lie with local health systems. Care and treatment responsibilities of the research teams end with appropriate access being provided through national systems.

Decisions on how these obligations are to be met are best made for each specific trial before they start to recruit participants. Those decisions should be made through a transparent and participatory process that involves all research stakeholders (see Guidance Point 2). This process should explore options and determine the core obligations applicable to the given situation, in terms of the level, scope and duration of the care and treatment package, the equity in eligibility to access services, and the responsibility for provision and delivery.

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

¹² WHO 2019 Update of recommendations on first- and second-line antiretroviral regimens. WHO/CDS/HIV/19.15

The care and treatment package

A care and treatment package for all study participants will be context specific. Typically, however, it will include some or all of the following types of items, depending on the nature of the research, the setting and the consensus reached by all interested parties prior to the trial:

- ▶ Information, counselling and HIV testing, including the offer of voluntary partner services.
- ▶ Antiretroviral therapy in line with WHO guidance,¹³ including drug resistance testing, for any participant who acquires HIV during trials of interventions with antiretroviral activity.
- ▶ HIV preventive methods and means (see Guidance Point 11).
- ▶ Adherence and retention in care support services for HIV treatment and prevention interventions.
- ▶ Access to comprehensive sexuality education and sexual and reproductive health and rights services including contraception choices.
- ▶ Antenatal and postnatal care for pregnant women and their children
- ▶ Prevention of mother-to-child transmission of HIV, viral hepatitis and syphilis.
- ▶ Diagnosis and treatment for other sexually transmitted infections.
- ▶ Prevention, diagnosis and treatment of tuberculosis.
- ▶ Prevention, diagnosis and treatment of opportunistic infections.
- ▶ Prevention, diagnosis and treatment of comorbidities, including mental health and cervical cancer screening.
- ▶ Nutritional support.
- ▶ Palliative care, including pain control, spiritual care, and referral to social and community support.
- ▶ Services for victims of violence.

Care and treatment in protocol and informed consent process

Agreements on who will finance, deliver and monitor care and treatment should be documented in the protocol. Connection to prompt treatment may require additional resources. Plans for care and treatment for HIV should be clearly explained, available for consultation and understood by participants during the informed consent process.

Participants who have been exposed to antiretrovirals (such as PrEP) or an experimental product with antiviral activity are at increased risk of acquiring HIV that is resistant to some antiretroviral medicines. Regardless of the individual participant's adherence to the package of prevention (see Guidance Point 11), research teams must ensure that drug resistance testing is an integral part of the package of care and that treatment is adjusted accordingly.

¹³ WHO 2019 Update of recommendations on first- and second-line antiretroviral regimens. WHO/CDS/HIV/19.15

Guidance Point 13: trial monitoring

Researchers and sponsors should ensure that monitoring throughout the duration of the trial covers the ethical requirements of research with humans. These requirements include, but are not limited to, safety and efficacy of the interventions, the initial and continuing quality of the informed consent process and confidentiality of data, access to WHO-recommended prevention methods and to WHO-recommended care and treatment for those who test positive for HIV infection during screening or who acquire HIV during the trial.

Methods for monitoring

Methods for monitoring should be designed and agreed upon by the community-government-investigator-sponsor partnership. The appropriateness of the monitoring plan should be approved by the research ethics committees.

Monitoring safety and efficacy of the interventions

HIV prevention trials should include a data safety monitoring board (DSMB). The DSMB is an independent data-monitoring group that is responsible for safeguarding the interests of trial participants by assessing the safety of the interventions during the trial. The DSMB will monitor and review participant safety in the trial (including evidence for treatment harm). It will review participant recruitment, accrual, retention, treatment discontinuation, trial withdrawal, serious breaches, and protocol deviations that require exclusion of the participant from the per-protocol analysis. The DSMB will use the accumulating clinical data to differentiate reported safety events associated with the trial interventions from those with other aetiologies.

The DSMB will have access to periodic, unblinded analyses that include the number of new HIV infections observed in each arm of the trial. They will monitor efficacy based on pre-planned interim data analyses and may recommend to the sponsors that a trial is terminated if pre-specified levels of efficacy are reached, or if analyses show that continuation of the trial is futile.

Researchers should provide the research ethics committee with a charter that defines the composition, responsibilities and procedures of the DSMB .

Monitoring quality of informed consent process

The adequacy of recruitment and informed consent processes, including evaluations of the comprehension of information among participants, should be monitored. The value of informed consent depends primarily on the ongoing quality of the process by which it is conducted, and not solely on the structure and content of the informed consent document. The informed consent process should be designed and monitored to empower participants to allow them to make appropriate decisions about continuing or withdrawing from the study. Special attention should be given to ensure that individuals are aware of their right to withdraw from a trial without any penalty, and that they are free to do so.

Monitoring access to WHO recommended standards of prevention

In addition to reviewing documentation around consent and treatment, the trial monitoring should collect some basic information about the volume, uptake and the quality of prevention services, such as the number of condoms distributed, the approach to ensure that PrEP was available and other metrics. Similarly, there are many ways in which risk reduction interventions (counselling and access to means of HIV prevention) can be conducted, with some methods being more effective than others in conveying the relevant information and reducing risk of HIV exposure for different individuals and study populations.

Monitoring of care and treatment

Participants may test positive for HIV infection or acquire HIV during the trial. Researchers and sponsors have an obligation to ensure access to care and treatment both before the trial starts and during the trial. They should ensure that any person who acquires HIV infection or is found to be living with HIV is connected to immediate treatment. This process should be monitored carefully.

Other relevant issues to monitor

Monitoring should include quality assurance of gender- and culture-sensitive counselling services, confidentiality mechanisms, redress mechanisms for complaints and appropriate procedures for adolescents. It also should cover the welfare of participants throughout the trial, including the discontinuation of participation in case of adverse reactions, untoward events or changes in clinical status. Research protocols also might include ongoing independent monitoring of a trial in relation to its impact on the contexts of the vulnerability of communities participating in the study.

Independent ombudsperson

Consideration could be given to the appointment of an independent ombudsperson to handle any complaints from participants related to the conduct of the trial and to suggest appropriate responses.

Guidance Point 14: post-trial access and dissemination

As part of the protocol, researchers and trial sponsors should have an agreed plan for post-trial access. In principle, trial sponsors should provide ongoing provision of HIV preventive products that have been demonstrated to be efficacious to all trial participants. The research team also has a special obligation to ensure the timely dissemination of study progress at regular intervals and to report and publish the final results in peer-reviewed journals. Dissemination of progress updates and results to national authorities, local communities and study participants should be a priority and occur before or contemporaneously with international dissemination

Provision of proven effective Phase 2b/3 products

Researchers and sponsors should consult with key stakeholders—such as representatives of local health authorities, communities and nongovernmental organizations—in advance of the trial. Together, they should make an agreed plan that determines everyone's responsibility in providing continued access to the proven efficacious HIV intervention product after the trial. Sponsors should provide continued access to the proven efficacious intervention for the intervention group and access to the placebo group once the intervention has been demonstrated to be efficacious. At the same time, the obligation to provide participants with post-trial access depends on several factors and may vary. The obligation to provide post-trial access is greater when there are no acceptable alternatives available in the health-care system, or when withholding the HIV preventive method implies a significant reduction in the quality of life that participants have otherwise experienced during the study. Furthermore, not all HIV preventive products that are tested in trials are on a pathway to regulatory approval, such as some vaccines or monoclonal antibodies. The social value of these studies may lie in their potential to inform future studies and not in their potential to bring the product to market immediately after the trial has ended.

Scaling up proven effective Phase 2b/3 products

Before trials commence, health and research communities building HIV prevention product development programmes should initiate a process of discussion and negotiation about how products will be made available to the country in which the products are tested if the HIV preventive intervention is efficacious. This process should carry on throughout the course of the research, and it should also include the other benefits resulting from the research. This discussion should address issues such as:

- ▶ Payments, royalties, subsidies, technology and intellectual property.
- ▶ Distribution costs, channels and modalities. This includes delivery strategies, target populations, the number of doses made available to the country, preferential pricing, demand estimates and supply chain requirements.

Representatives of relevant countries—such as representatives of the executive branch, health ministry, local health authorities, relevant scientific and ethical groups, community advisory mechanisms and other key stakeholders—should be involved in the discussion.

Some argue that fair benefits to the population where clinical trials are being conducted need not include making successful products of the research available to that population. Critics contend that it is paternalistic to specify the benefits, and that

the country may identify other benefits that have a higher priority. Given the severity of the epidemic, however, making a successful HIV prevention product or intervention reasonably available to the population where it was tested can be sustained as a basic ethical requirement (see Guidance Point 1).

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

- ▶ Ongoing communication with regulatory agencies to ensure the timely licensing of proven safe and efficacious methods that require regulatory approval.
- ▶ Planning for capacity-building, including transfer of technology, to mass produce an effective HIV prevention product well in advance of product licensing in order to minimize manufacturing delays.
- ▶ Preparing the infrastructures needed for delivery of new products in advance through existing distribution systems used for other currently available HIV prevention products, such as male and female condoms or prophylaxis to prevent mother-to-child transmission of HIV, viral hepatitis and syphilis.
- ▶ Instituting advance purchase commitments or other supply side planning to deliver product for people and populations that have been identified as being the first to enjoy the benefits of a new, proven HIV prevention intervention.

Information about results

To respect and recognize the contribution to clinical research of trial participants and their communities, researchers should inform them of the trial results and their implications, in an appropriate way such that the results are understood by the community as a whole, whether the intervention does or does not demonstrate efficacy, or if the trial is stopped prematurely.

Dissemination

Researchers should adequately report the results of their research and make them publicly available. They should also comply with the 2016 FAIR Guiding Principles for scientific data management and stewardship and make their data findable, accessible, interoperable and reusable.¹⁴ The timing of dissemination is essential: ideally, participants, communities and governments are informed of research results before others. This process is particularly important for studies that involve multiple sites.

¹⁴ FAIR Guiding Principles for scientific data management and stewardship, 2016. <https://www.nature.com/articles/sdata201618>

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Glossary

AIDS: Acquired immunodeficiency syndrome (UNAIDS Terminology guidelines 2015 https://www.unaids.org/sites/default/files/media_asset/2015_terminology_guidelines_en.pdf).

Ancillary care: “Ancillary-care obligations are positive obligations to provide care that participants need but that is required neither to successfully answer the researchers’ scientific question nor to avoid or mitigate harm resulting from participation in the research.”¹⁵

Assent: Children and adolescents who are legally minors cannot give legally valid informed consent, but they may be able to give assent. To give assent means that the child or adolescent is meaningfully engaged in the research discussion in accordance with his or her capacities and agrees to participate.¹⁶

Benefits: The level of support, care and treatment provided to potential and enrolled participants.

Biobanking: : “... collections of human biological materials (biospecimens) linked to relevant personal and health information (which may include health records, family history, lifestyle and genetic information) and held specifically for use in health and medical research.”¹⁷

Care and treatment (HIV-related): The level of care and treatment provided to all research participants who test positive for HIV infection during screening or who acquire HIV during the trial.

Child: Every human being below the age of 18 years unless, under the law applicable to the child, majority is attained earlier.

Community: Defining the relevant community for consultation and partnership is a complex and evolving process that should be discussed with relevant local authorities. As more groups and people define themselves as part of the interested community, the concept needs to be broadened to civil society in order to include advocates, media, human rights organizations, national institutions and governments, as well as researchers and community representatives from the trial site.

Confidentiality: “Prevention of disclosure, to other than authorized individuals, of a sponsor’s proprietary information or of a subject’s identity.”¹⁸

Contexts of vulnerability: The social and political contexts of vulnerability of participating communities and populations.

Data banking: “The systematic collection of data, whether individually identifiable, re-identifiable or non-identifiable”¹⁹

¹⁵ Participants in the 2006 Georgetown University Workshop on Ancillary-Care Obligations of Medical Researchers Working in Developing Countries. The ancillary-care obligations of medical researchers working in developing countries. PLoS Med. 2008;5(5):e90.

¹⁶ International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.

¹⁷ National Health and Medical Research Council (Australia) Biobanks Information Paper 2010

¹⁸ Guideline for good clinical practice E6(R2). Step 5. Committee for Human Medicinal Products, 1 December 2016 (EMA/CHMP/ICH/135/1995; https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf).

¹⁹ National Health and Medical Research Council (Australia) National Statement on Ethical Conduct in Human Research 2007 and updated 2018

Data Safety Monitoring Board: The DSMB is an independent data-monitoring group that may be established by those responsible for trial conduct to monitor the progress of a clinical trial with particular focus on potentially arising safety issues.

Development plan: A plan for the pathway of a product to manufacturing, market access and implementation after early proof of concept.

Development partners: Persons, companies or institutions involved in the development plan.

Dissemination: The act of spreading news, information and research results to stakeholders of the trial.

Gender: “Refers to the social attributes and opportunities associated with being male and female and the relationships between women and men and girls and boys, as well as the relations between women and those between men. These attributes, opportunities and relationships are socially constructed and are learned through socialization processes. They are context/time-specific and changeable. Gender determines what is expected, allowed and valued in a woman or a man in a given context. In most societies, there are differences and inequalities between women and men in responsibilities assigned, activities undertaken, access to and control over resources, as well as decision-making opportunities.”²⁰

Gender identity: “A person’s deeply felt internal and individual experience of gender, which may or may not correspond with the sex assigned at birth. It includes both the personal sense of the body—which may involve, if freely chosen, modification of bodily appearance or function by medical, surgical or other means—as well as other expressions of gender, including dress, speech and mannerisms.”²¹

Gender-diverse person: A person whose “gender identity, role or expression differs from the cultural norms prescribed for people of a particular sex.”²²

Harms: Participation in HIV prevention trials may involve physical, social, economic, legal and psychological harms.

Human immunodeficiency virus (HIV): HIV is a virus that weakens the immune system, ultimately leading to AIDS. (UNAIDS Terminology guidelines 2015 UNAIDS Terminology Guidelines - 2015 https://www.unaids.org/sites/default/files/media_asset/2015_terminology_guidelines_en.pdf).

HIV prevention trial: A clinical trial that tests HIV prevention methods.

Informed consent: “A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects

²⁰ Concepts and definitions. In: UN Women [Internet]. The United Nations Entity for Gender Equity and the Empowerment of Women (UN Women); c2020 (<http://www.un.org/womenwatch/osagi/conceptsanddefinitions.htm>).

²¹ UNAIDS terminology guidelines. Geneva: UNAIDS; 2015.

²² Key terms and concepts in understanding gender diversity and sexual orientation among students. American Psychological Association; 2015 (<https://www.apa.org/pi/lgbt/programs/safe-supportive/lgbt/key-terms.pdf>).

of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form."²³

Key populations: "UNAIDS considers gay men and other men who have sex with men, sex workers and their clients, transgender people, people who inject drugs and prisoners and other incarcerated people as the main key population groups. These populations often suffer from punitive laws or stigmatizing policies, and they are among the most likely to be exposed to HIV. Their engagement is critical to a successful HIV response everywhere—they are key to the epidemic and key to the response. Countries should define the specific populations that are key to their epidemic and response based on the epidemiological and social context. The term key populations at higher risk also may be used more broadly, referring to additional populations that are most at risk of acquiring or transmitting HIV, regardless of the legal and policy environment."²⁴

Manufacturer: A company that produces goods in large numbers.

Placebo (product): "An inert substance . . . that is provided to research participants with the aim of making it impossible for them, and usually the researchers themselves, to know who is receiving an active or inactive intervention."²⁵

Pre-exposure prophylaxis (PrEP): "Pre-exposure prophylaxis refers to antiretroviral medicines prescribed before exposure (or possible exposure) to HIV. Several studies have demonstrated that appropriate use of antiretroviral medicines is effective in both men and women for reducing the risk of acquiring HIV infection through sexual or injection transmission."²⁶

Prevention package: "A collection of services for human immunodeficiency virus (HIV) prevention made available to all participants in an HIV prevention research project."²⁷

Privacy: Someone's right to keep their personal matters and relationships secret.

Product development plan: See development plan

Post-trial access: "Provision of or access to an investigational product after research ends."²⁸

Randomized controlled trial: "A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias."²⁹

²³ Guideline for good clinical practice E6(R2). Step 5. Committee for Human Medicinal Products, 1 December 2016 (EMA/CHMP/ICH/135/1995; https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf).

²⁴ UNAIDS terminology guidelines. Geneva: UNAIDS; 2015.

²⁵ International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.

²⁶ From UNAIDS terminology guidelines. Geneva: UNAIDS; 2015.

²⁷ Brown B, Sugarman J; HPTN Ethics Working Group. Ethics guidance for research. Revised February 2020. HPTN; 2020 ([HPTNEthicsGuidanceDocument_2.26.20.pdf](https://www.hptn.org/sites/default/files/HPTNEthicsGuidanceDocument_2.26.20.pdf)).

²⁸ Brown B, Sugarman J; HPTN Ethics Working Group. Ethics guidance for research. Revised February 2020. HPTN; 2020 ([HPTNEthicsGuidanceDocument_2.26.20.pdf](https://www.hptn.org/sites/default/files/HPTNEthicsGuidanceDocument_2.26.20.pdf)).

²⁹ Glossary. In: National Institute for Health and Care Excellent (NICE) [Internet]. London: NICE; c2020 (<https://www.nice.org.uk/glossary?letter=r>).

Scientific and ethics review: The process undertaken by independent scientific review committees and research ethics committees established by recognized authorities that leads to approval or rejection of research protocols.

Screening process: Researchers who look for specific conditions or characteristics of a participant that can lead to inclusion or exclusion in a trial in accordance with pre-defined criteria.

Standard of prevention: The level of prevention provided to participants in an HIV prevention trial. See also *WHO recommended package of prevention methods*

Study populations: The population of participants who are drawn from the community

Trial sponsor: "An individual, company, institution or organization [that] takes responsibility for the initiation, management, and/or financing of a clinical trial."³⁰

Trial monitoring: "The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."³¹

Stakeholders: "People or organizations who have an interest in the research or are affected by its outcomes."³²

Vulnerability: See contexts of vulnerability

WHO recommended package of prevention methods: The package that the World Health Organization recommends as HIV prevention options and the prevention guidance that WHO has provided for a range of populations.

³⁰ Guideline for good clinical practice E6(R2). Step 5. Committee for Human Medicinal Products, 1 December 2016 (EMA/CHMP/ICH/135/1995; https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf).

³¹ Guideline for good clinical practice E6(R2). Step 5. Committee for Human Medicinal Products, 1 December 2016 (EMA/CHMP/ICH/135/1995; https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf).

³² Brown B, Sugarman J; HPTN Ethics Working Group. Ethics guidance for research. Revised February 2020. HPTN; 2020 ([HPTNEthicsGuidanceDocument_2.26.20.pdf](https://www.hptn.org/sites/default/files/HPTNEthicsGuidanceDocument_2.26.20.pdf)).

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