



# Standards of prevention in HIV prevention trials

Consultation report and  
recommendations



27 to 29 March 2009

Speake Resort  
Munyonyo  
Kampala, Uganda



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Convened by the Global Campaign for Microbicides,  
the Joint United Nations Programme on HIV/AIDS, and  
the United States Centers for Disease Control and Prevention

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## Acronyms and abbreviations

ARV	Anti-retroviral
CDC	US Centers for Disease Control and Prevention
CIOMS	Council for International Organizations of Medical Sciences
DSMB	Data Safety and Monitoring Board
GCM	Global Campaign for Microbicides
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
HSV-2	Herpes simplex virus-2
iPrEX	Pre-Exposure Prophylaxis Initiative
IRB	Institutional Review Board
MDP	Microbicides Development Programme
PrEP	Pre-exposure prophylaxis
RCT	Randomised controlled trial
STI	Sexually transmitted infection
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
US	United States
WHO	World Health Organization

## Table of contents

<b>Acknowledgments</b> .....	2
<b>Acronyms and abbreviations</b> .....	3
<b>Background</b> .....	6
<b>Consultation</b> .....	8
<b>HIV prevention trials</b> .....	9
<b>Bioethical frameworks and standards of prevention</b> .....	10
Principalism .....	10
Standard of care .....	10
Therapeutic obligation and clinical equipoise .....	11
The duty of rescue .....	11
Discussion and limitations .....	11
<b>Evolution of UNAIDS/WHO guidance on HIV prevention trials</b> .....	12
Considerations in 2000 guidance .....	12
Access to treatment .....	12
Standard of prevention .....	12
Revisions in 2007 guidance .....	14
Standard of prevention .....	14
Implementation and decision-making .....	14
Implications for trials .....	14
<b>Interpreting and implementing what “works”</b> .....	16
When is an approach “proven”? .....	16
When is a method “established”? .....	17
When should a new method be added to the standard HIV prevention package? .....	17
Discussion .....	18
<b>Stakeholder perspectives</b> .....	19
<b>Prevention trial realities</b> .....	22
<b>What “standard of prevention” is being provided in HIV prevention trials now?</b> .....	24
<b>Participatory exercises</b> .....	26
When should a new product be included in the prevention package? .....	26
Providing access to HIV prevention in a research setting .....	26

<b>Key issues for trials and beyond</b> .....	<b>28</b>
Innovation and sustainability .....	28
New products versus established products .....	28
Undue inducement .....	29
“Providing” a service .....	29
Meeting research needs and objectives .....	29
Developing a core prevention package .....	30
Authority and responsibility .....	30
Trial ethics in context .....	30
Individual rights and public health needs .....	31
Access and sustainability of trial products .....	31
<b>Points of agreement and disagreement</b> .....	<b>32</b>
<b>Need for additional guidelines and criteria</b> .....	<b>34</b>
Consultation and negotiation .....	34
Balancing individual rights with public health needs .....	35
<b>Looking ahead</b> .....	<b>36</b>
<b>References</b> .....	<b>37</b>
<b>Appendix: List of participants</b> .....	<b>38</b>

## Background

Research into biomedical HIV prevention technologies has begun to identify several new partially effective interventions. For example, trials completed in 2006 showed that adult male circumcision reduces the risk that men will acquire HIV from heterosexual sex by nearly 60 percent.<sup>1,2,3</sup> Recent findings from Thailand suggested that a combination vaccine regimen could reduce the risk of HIV acquisition by approximately 30 percent, although the duration of the protection is still uncertain.<sup>4</sup> On the horizon, a number of safety and effectiveness trials testing oral tenofovir and Truvada regimens as pre-exposure prophylaxis (PrEP) in different populations in a range of settings will begin reporting results in late 2010.

These developments are encouraging in the long search for new HIV prevention tools. However, they pose new challenges and dilemmas for ongoing and future trials of biomedical HIV prevention interventions. HIV prevention trials provide all study participants with a prevention package designed to reduce their risk of HIV infection and, as new prevention technologies and interventions emerge, it will be important to determine when to include them as part of the “standard of prevention” offered to all trial volunteers. The most recent guidance from the 2007 UNAIDS/WHO guidance document *Ethical Considerations in Biomedical HIV Prevention Trials*—states that all study participants must be ensured access to all “state-of-the-art” prevention methods:

Researchers, research staff, and trial sponsors should ensure, as an integral component of the research protocol, that appropriate counselling and access to all state-of-the-art HIV risk

reduction methods are provided to participants throughout the duration of the biomedical HIV prevention trial.<sup>5</sup>

With regard to when to include new prevention technologies as “state-of-the-art,” the guidance includes a procedural element that states:

New HIV-risk-reduction methods should be added, based on consultation among all research stakeholders including the community, as they are scientifically validated or as they are approved by relevant authorities.<sup>5</sup>

The 2007 UNAIDS/WHO guidance document lists key elements of a “state-of-the-art” package in the commentary to this guidance point, with the understanding that this package will evolve as new prevention modalities are found efficacious. The document does not address the question of what it means for a new method to be “scientifically validated” or “approved by relevant authorities” since these conditions are defined differently by different regulatory and normative bodies. With respect to the negotiations with stakeholders, the commentary suggests that they should “take into consideration feasibility, expected impact, and the ability to isolate the efficacy of the biomedical HIV modality being tested, as other prevention activities improve.”<sup>5</sup> This leaves numerous practical questions about how to translate this ethical guidance into practice, both within individual trials and within the overall context of HIV prevention research. For example:

- What are investigators’ ethical obligations for ensuring access to prevention for participants in HIV prevention studies?



- When and under what circumstances are researchers ethically obligated to make a new prevention tool available to study participants in a future HIV prevention trial?
- Under what circumstances, if any, would it be necessary to stop or modify an on-going HIV prevention trial because a method is shown to be effective in another trial?
- What impact will adding new prevention modalities have on the ability of future trials to evaluate the efficacy of the HIV prevention tools they are testing?

- Should the continued addition of partially effective tools to the standard prevention package make it otherwise impossible to test new technologies, would the urgent public need for additional HIV prevention technologies ever justify reconsidering the level and type of prevention modalities provided to trial participants?

In the face of new and emerging results from HIV prevention trials, it is critical that the field reflect creatively and thoughtfully on these issues to develop practical approaches that incorporate the perspectives of multiple stakeholders.

## Consultation

In March 2009, the Global Campaign for Microbicides (GCM), the Joint United Nations Programme on HIV/AIDS (UNAIDS), and the US Centers for Disease Control and Prevention (CDC) jointly convened a consultation to catalyse discussion and to build consensus about how to address these new challenges associated with designing and conducting HIV prevention trials. This consultation, “Standards of Prevention in HIV Prevention Trials” held in Kampala, Uganda, brought together nearly 60 researchers, advocates, ethicists, donors, policymakers and regulators working in HIV prevention. The three sponsoring agencies brought complementary perspectives and expertise to these complex questions. GCM has a long history of working to build consensus around the complex practical and ethical dilemmas in clinical testing of HIV prevention interventions, especially microbicides. As the key international agency advocating for universal access to HIV prevention, treatment, care and support, UNAIDS has facilitated and supported many efforts to develop guidance on ethical and participatory clinical trial conduct and help diverse groups find common ground on important ethical issues in biomedical HIV prevention trials. The CDC is the leading normative public health agency in the United States and it also sponsors a number of biomedical HIV prevention trials around the world, especially in the area of pre-exposure prophylaxis (PrEP).

The consultation was designed to build on the existing guidelines from UNAIDS and the World Health Organization (WHO), to explore challenges in operationalising such guidance, and to derive a set of criteria to help researchers, advocates, donors, policymakers, and regulators apply the guidance in practice. This report summarizes the key

background presentations, discussions, and exercises, and the main issues that emerged. It is organised around the following main sections:

- HIV prevention trial characteristics that determine how and where these trials can be conducted.
- Key bioethical frameworks and existing ethical guidance, and what each suggests about standards of prevention.
- Evolution of the UNAIDS/WHO ethical guidance on HIV prevention trials, focusing specifically on guidance point 13 in the new UNAIDS/WHO guidance document which concerns standards of prevention.
- Evidence for current HIV prevention approaches as background for assessing and setting standards for what “works.”
- Key stakeholder perspectives on current and emerging HIV prevention methods.
- Scientific and political realities faced by ongoing and planned prevention trials in the face of emergent data.
- Standards of prevention currently being provided in HIV prevention trials.
- Participatory exercises from the consultation designed to take participants through decision-making processes.
- Key issues for HIV prevention trials, summarizing some of the main debates and discussions.
- Points of agreement, disagreement, and areas for further guidance.

This report concludes with the points of agreement and disagreement as developed by the meeting participants. It also identifies some outstanding issues and suggests additional steps to continue efforts to address these challenges while at the same time facilitating urgently needed research on new HIV prevention methods.

## HIV prevention trials

Several requirements of HIV prevention trials make them unusually difficult to design and implement. HIV prevention trials enroll healthy people at risk of HIV infection, so all participants must be provided with an HIV prevention package. This package generally includes at least safer sex counselling, condoms, and testing and treatment for sexually transmitted infections (STIs), with some trials providing other interventions. HIV prevention trials are endpoint driven, meaning that the trial's size and its statistical power are based on the number of HIV seroconversions that are observed in the trial population. In order to have the power to properly evaluate effectiveness, the trials therefore need to take place in settings and populations with a relatively high HIV incidence rate. As currently designed, most trials must enroll large numbers of participants in communities with an annual HIV incidence rate of at least 3 to 4 percent in order to be feasible. Most HIV prevention efficacy trials thus are multi-site and enroll between 2,000 and 10,000 participants. The Thai RV144 prime-boost vaccine trial enrolled more than 16,000 participants.

Depending on the prevention modality and/or route of transmission being tested, some trials can enroll only subsets of the population, such as women (in the case of vaginal microbicide trials), people who inject drugs, or men who have sex with

men. In many settings, these populations can be difficult to recruit, enroll and retain in trials. Many trials also have relatively narrow enrollment criteria that may leave important safety and efficacy questions unanswered. In many microbicide trials, for example, participation is limited to women above a certain age or women who are not pregnant, which means that these trials will not address safety or efficacy in young women or during pregnancy.

All new biomedical HIV prevention methods being tested (topical microbicides, oral PrEP, or vaccines) will likely be at best partially effective, meaning they are likely to reduce but not eliminate an individual's risk of HIV acquisition. (Current trials are powered to detect a reduction in incidence between the active and control groups of 40 to 60 percent). Due to the cost and complexities of trials, and the lack of surrogate endpoints, some trials are being designed as Phase 2B screening trials rather than full Phase 3 trials to demonstrate efficacy. This means that the Phase 2B trials currently under way may not provide conclusive evidence of whether a new product or intervention "works" and should be included in the prevention package. Licensure of a new product or relabeling of an existing product for a new indication may thus require additional trials. Even if there is evidence that a product is effective, it is unlikely that it will be licenced or made available for several years at least.

# Bioethical frameworks and standards of prevention

Standard of prevention is often framed as an ethical issue, but it is not always clear what ethical reasoning informs guidelines and recommendations about when to include new HIV prevention tools in the standard prevention package. In broad terms, HIV prevention researchers must recognise the potential vulnerability of study participants and must design studies that minimise volunteers' risks and maximise the benefits of their participation. Therefore, it is often assumed that researchers have an ethical obligation to provide all study participants with access to established and effective HIV prevention and care services. Guidelines like those in the 2007 UNAIDS/WHO guidance document, for example, state that participants in an HIV prevention trial must be provided with a comprehensive risk reduction package.

To review what different ethical frameworks would imply for researchers' responsibilities, a panel of four ethicists outlined some of the key ethical frameworks often applied to HIV prevention trials: principlism, standard of care, therapeutic obligation and equipoise, and duty of rescue.

## Principlism

In the 1960s, following a series of research scandals, the United States government established a commission charged with developing a set of guidelines for the design, review, and conduct of research involving human subjects. That document, known as the Belmont Report, established three key ethical principles that should guide the design and conduct of research trials:

1. Respect for persons—treating all study participants with courtesy and respect.
2. Beneficence—maximising benefits and minimising risks to research participants.

3. Justice—ensuring that study participants or trial communities are not exploited.<sup>6</sup>

Under the principle of beneficence, researchers are to provide trial participants with access to all proven safe and effective HIV prevention tools, and they cannot deny participants access to HIV prevention tools that already exist within the trial community. This obligation has limits, however, and defining the limits and the circumstances when they would be applied was a key goal of the consultation. For example, many ethicists believe that researchers should provide male circumcision if they can afford to do so, but that they are not obligated to provide circumcision services until this prevention tool has become an established and accepted intervention within the larger community.

## Standard of care

The “standard of care” argument maintains that it is unethical to conduct a clinical trial in which some participants receive a level of care (or prevention) that falls below the established standard of care. Whether the established standard of care is defined as the best-proven intervention available anywhere in the world or the best services available locally, however, continues to be a source of considerable debate and confusion.

Most ethicists and researchers believe that providing the local standard of care is often inadequate, and allowing trials to define the prevention package in terms of local standards of care would require researchers to provide few, if any, HIV prevention tools.<sup>7</sup> However, insisting that researchers provide a global, state-of-the-art standard of care has its own challenges. Most ethicists instead believe that researchers should

provide as high a level of care and prevention as possible, so long as doing so would not place an impossible burden on researchers or require investigators to provide a level of care that is unachievable or unsustainable.<sup>8</sup>

### **Therapeutic obligation and clinical equipoise**

Therapeutic obligation is the notion that physicians—and by extension physician-researchers have an obligation to do what is best for their patients. Randomised controlled clinical trials such as vaccine or microbicide studies, by their very nature, violate a physician's therapeutic obligation unless there is genuine uncertainty as to whether the treatment under investigation is no better or no worse than existing standards of care. This state of uncertainty is called clinical equipoise, which implies that research trials are ethical only when there is “no consensus within the expert clinical community about the comparative merits of the alternatives to be tested.”<sup>9</sup>

Although the concept of equipoise would appear to obligate researchers to provide participants with all known and effective HIV prevention tools, some ethicists question the appropriateness of grounding obligations to research participants in the physician's therapeutic obligation. Researchers are not primary-care physicians and the clinical services provided in HIV prevention trials are different from the types of medical care that an individual normally receives.<sup>10,11</sup>

### **The duty of rescue**

The last of the ethical frameworks discussed here, the duty of rescue, derives from the biblical parable of the Good Samaritan. In the same way that

the principle of beneficence requires researchers to maximise the benefits and minimise the risks of trial participation, the duty of rescue implies that researchers have an obligation to provide at least some care beyond that which is required to conduct the study. As with the principle of beneficence, however, this obligation is not limitless. In places where public health clinics are overburdened, under-funded, or do not exist, researchers are often called upon to provide “care which is not required to make a study scientifically valid, to ensure a trial's safety, or to redress research injuries.”<sup>12</sup> So long as the cost of this care does not threaten the trial itself, some would argue that there is no compelling reason why the researchers do not have an obligation to provide as many additional medical and social services to study participants as possible.

### **Discussion and limitations**

As the panelists pointed out, these ethical guidelines and frameworks help guide decision-making but do not establish clear criteria as to the types and intensity of prevention services that must be provided to participants in HIV prevention trials. Particularly when considering new HIV prevention tools (like male circumcision), tools that are not readily available in many communities (like the female condom), or tools that are protective only for very specific key populations at higher risk of HIV exposure (like clean needles for people who inject drugs), there is still considerable debate and disagreement about the nature and extent of researcher and donor obligations. Ethical guidelines and frameworks can provide broad principles but rarely provide a “one size fits all” set of recommendations on the types and levels of prevention and care services within individual research trials.

# Evolution of UNAIDS/WHO guidance on HIV prevention trials

Ethical guidelines on biomedical research and practice generally do not provide a great deal of guidance that is operational or relevant to clinical trials of new HIV prevention technologies (see Box 1). The majority of ethical guidelines were developed to address issues in clinical practice or in clinical trials of new medical treatments for people who are already ill. As described earlier, HIV prevention trials differ from other types of clinical trials in a number of important ways. By design, these trials must enroll and follow-up large numbers of otherwise-healthy participants, generally in resource-poor settings. Cultural contexts and social factors affect participants' adherence to product use and their risk behaviors.<sup>13</sup> Participants in prevention trials may also experience psychosocial harms directly attributable to stigma associated with HIV, including being ostracized, loss of employment and health insurance, and intimate-partner violence.<sup>14,15</sup> These broader risks and realities are generally not addressed directly in existing ethical guidance.

Recognising these gaps, and the urgent need for biomedical HIV prevention trials, UNAIDS played a key role in developing ethical guidance on HIV prevention trials, starting with the publication in 2000 of *Ethical Considerations in HIV Preventive Vaccine Research*. A revision of these guidelines published in 2007 expanded the scope to include other HIV prevention technologies in addition to vaccines and considered new issues that had emerged or evolved since 2000. Dr. Ruth Macklin, a member of both the 2000 and the 2007 UNAIDS committees, outlined how the 2007 guidelines evolved from the older guidance document through examining recommendations and other developments since 2000. Her presentation focused

in particular on Guidance Point 13, the main point being considered at the March 2009 consultation.

## Considerations in 2000 guidance

### Access to treatment

The main area of controversy during the development of the 2000 guidelines was the type and level of care and treatment for participants in HIV vaccine trials who became infected with HIV during the study. During a series of consultations, a range of views emerged about what types and levels of care and treatment would be “ethical.” The resulting compromise was that “care and treatment for HIV/AIDS... should be provided to participants... with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country in light of [circumstances specified].”<sup>16</sup> While this point reflected the diverse perspectives that existed at the time, it did not provide researchers with clear operational guidance on what to do.

### Standard of prevention

Interestingly, the issue of standard of prevention (referred to as “risk reduction” and addressed in Guidance Point 14 in the 2000 guidance document) was not particularly controversial during the drafting of the 2000 guidelines. Counselling and condoms were offered in all trials, and concerns that researchers might have a conflict of interest between offering risk reduction services and the need for HIV “endpoints” had faded. A controversy did emerge later when the AIDS-VAX trial did not offer participants—people injecting drugs in Thailand and the United States—clean injecting equipment.

## What do different ethical guidelines tell us about standards of prevention?

While most ethical guidance deals with treatment or research on treatment, it is useful to look at how the language in these documents can inform how to address ethical questions in HIV prevention trials. These guidelines reflect a lack of consensus and ongoing debate among ethicists about what should guide decision-making and how these principles should be applied.

### Declaration of Helsinki (2008) paragraph 32<sup>17</sup>

- The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the *best current proven intervention*.
- Use of placebo or no treatment is acceptable in studies...where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm.

### Council for International Organizations of Medical Sciences (CIOMS) (2002) Guideline 11<sup>18</sup>

- Research subjects in the control group of a trial... should receive an established effective intervention.
- In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or “no treatment.”

### US National Bioethics Advisory Commission (2001) recommendation 2.2<sup>19</sup>

- Researchers and sponsors should design clinical trials that provide members of any control group with an established effective treatment, whether or not such treatment is available in the host country.
- Established means “has achieved widespread acceptance by the medical community (2001; 28).”

### Nuffield Council (2002)<sup>20</sup>

- Where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered is the best available intervention as part of the national public health system for that disease.

### UNAIDS/WHO (2000) Guidance Point 14<sup>16</sup>

- Appropriate risk-reduction counselling and access to prevention methods should be provided to all vaccine trial participants, with new methods being added as they are discovered and validated.

### UNAIDS/WHO (2007) Guidance Point 13<sup>5</sup>

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

## Revisions in 2007 guidance

In response to changing circumstances, the 2000 guidance document was revised during a consultative process that started in 2006. The scope was broadened from vaccines to include all biomedical HIV prevention trials. The availability of care and support had grown considerably, and new HIV prevention approaches were being introduced (male circumcision) and tested (PrEP and microbicides).

### Standard of prevention

In the 2007 document, Guidance Point 13 on standard of prevention broadens the concept of what should be provided to trial participants by specifying counselling and access to all “state-of-the-art” HIV risk-reduction methods. An early draft noted that access should be provided to “proven HIV prevention methods ... with new methods being added as they are discovered and validated.” After debate about the definitions of “proven” and “validated,” the final version of the guidance document strengthened this point by changing “proven HIV prevention methods” to “all state-of-the-art risk-reduction methods.” This prompted further debate—continued at the March 2009 consultation—about whether *all* “state-of-the-art” methods must be provided, including male circumcision and partially effective vaccines or microbicides if they became available. Doing so may make it logistically impossible—or at least infeasible—to design future vaccine or microbicide trials that are likely to generate clear and scientifically valid results.

### Implementation and decision-making

Guidance Point 13 proposes that the inclusion of new HIV risk reduction methods should be determined by a consultative process, stating:

New HIV-risk reduction methods should be added, based on consultation among all research stakeholders, including the community, as they are scientifically validated or as they are approved by relevant authorities.<sup>5</sup>

The commentary associated with this guidance point acknowledges the need to balance the prevention package with ensuring that a trial is sufficiently powered to generate a clear result, and proposes a procedural element for determining this balance:

Negotiations [among all research stakeholders, including the community] should take into consideration feasibility, expected impact, and the ability to isolate the efficacy of the biomedical HIV modality being tested, as other prevention activities improve.<sup>5</sup>

This commentary leaves open the question of what criteria would determine when a method is “scientifically validated” and what would happen if a method is approved by a regulatory (or other) authority in some countries but not in the country where a trial is being conducted. It also leaves open what should be provided in settings where the “state-of-the-art” prevention package may not be readily available or sustainable in the community following completion of the trial. The guidance calls for consultation with the community before, during, and after the initiation of a trial but it does not address how to resolve conflicts.

### Implications for trials

The 2007 guidance document intentionally drafted these guidance points to be flexible, allowing for changing circumstances and the diverse contexts of HIV prevention research. It proposes a process of negotiation involving a wide range of stakeholders that has rarely been attempted before. While this flexibility is important and useful, particularly in terms of engaging stakeholders and recognising the diversity of settings and perspectives, it leaves open and undefined many issues around both content and process for negotiating specific elements of prevention trials. There is little direction for researchers on how to make this procedural guidance operational, for example, including how to structure consultative



or other processes, who or what groups should be included within the rubric of “all research stakeholders including the community,” and whether that concept would vary in different settings or between different trials.

Finally, the guidance acknowledges situations where the obligation to provide individuals enrolled in trials with *all* state of the art prevention methods may make

trials so large, complex, and expensive that they are either infeasible or impossible and states that this must be taken into consideration in the decision on whether to add a new prevention modality. It does not deal with the implications of standard of prevention for the HIV prevention research field overall, which may make the overall search for new HIV prevention technologies unachievable.

## Interpreting and implementing what “works”

Guidance Point 13 requires that researchers provide all “state-of-the-art” interventions to all study participants, while the associated commentary calls for “proven” prevention methods. To implement such guidance it is important to determine when a prevention method would be considered “proven” safe and effective. An additional concern for implementation, and one raised throughout the guidance document, is determining when a safe and effective risk reduction measure is also established in a country or community. A key element in determining when an intervention is “proven” should be the quality and level of evidence.

To inform debate on when a prevention method would be “proven,” Dr. Janneke van de Wijgert summarized the levels of evidence that exist for HIV prevention methods: behavioural, biomedical, and structural. This review focused on behavioural and biomedical interventions designed to prevent sexual transmission of HIV. The analysis was based on a hierarchy of evidence as depicted in Figure 1, where

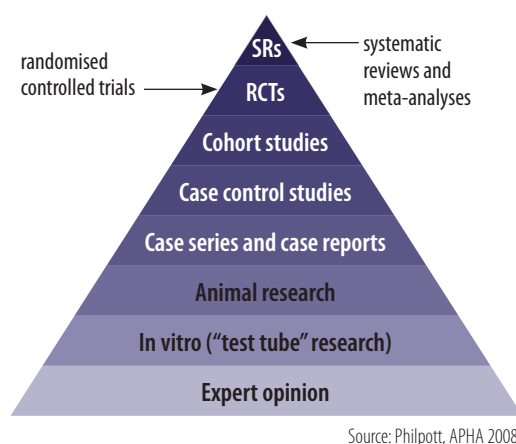


FIGURE 1. The evidence pyramid.

systematic reviews and meta-analyses provide the most compelling evidence of effectiveness, followed by randomised controlled trials, cohort studies, and so forth. Summarizing all of the data that was presented is beyond the scope of this report, but some of the highlights and key questions relevant to the standard of prevention are presented below.

### When is an approach “proven”?

Table 1 summarizes findings from randomised controlled trials looking at behavioural and biomedical interventions for HIV prevention. Only one trial has looked at the effectiveness of behavioural interventions using HIV incidence as an endpoint, and it showed no effect.<sup>a</sup> Many randomised controlled trials have been conducted looking at STI treatment as a way of preventing HIV transmission, but only one showed a reduction in HIV incidence (of 40 percent).<sup>21</sup> Oral post-exposure prophylaxis (PEP) cannot be evaluated in randomised controlled trials for ethical reasons, but even in the absence of this evidence it is assumed to work. In contrast, several trials have shown that male circumcision reduces HIV acquisition in men by nearly 60 percent.<sup>1,2,3</sup> Based on randomised controlled trials, the only intervention that has been *proven* to be effective in multiple trials is male circumcision.

Other HIV prevention interventions are supported by different levels of evidence. For example, a June 2000 expert consultation on the effectiveness of male condoms concluded that men and

a A recent review published in *AIDS* found that of 37 HIV prevention randomised controlled trials reporting on 39 unique interventions only 6 randomised controlled trials, all evaluating biomedical interventions, demonstrated definitive effects on HIV incidence. Almost 90% of HIV prevention trials had “flat” results. Padian N, McCoy S, Balkus J, Wasserheit J. Weighing the gold in the gold standard: challenges in HIV prevention research. *AIDS*. 2010; 24: 621–635.

**TABLE 1. Behavioral/biomedical intervention results from randomised controlled trials**

Intervention	RCTs completed*	RCTs effective
Behavior change†	1	0
Circumcision	4	3
STI treatment	7	1
Diaphragms	1	0
Microbicides‡	9	0
PrEP§	0	0
Vaccines¶	3	0

\* Only Phase 3 RCTs included with HIV incidence as endpoint.

† 8 other RCTs completed with behavioral/STI endpoints (none effective).

‡ Representing 5 experimental microbicides.

§ PEP cannot be evaluated in RCTs for ethical reasons.

¶ Representing 2 experimental vaccines.

women who use condoms consistently are at significantly reduced risk of acquiring HIV,<sup>22</sup> which was echoed in a WHO/UNAIDS information note.<sup>23</sup> Other systematic reviews have shown benefit of inconsistent condom use as well. For female condoms, polyurethane has been shown to be an effective barrier in the laboratory, and studies in Kenya, Thailand, and the United States have shown that female condoms are at least as effective as male condoms in preventing STIs. Several studies have also shown that providing female condoms increases levels of protected sex, suggesting that female condoms have both a direct and indirect effect in reducing rates of HIV transmission.<sup>24</sup>

Only one of seven randomised controlled trials of STI control or HSV-2 suppression to reduce HIV incidence showed an effect (40 percent) reduction of HIV incidence, and that trial was conducted in a concentrated epidemic.<sup>21,25</sup> However, strong biological evidence exists for a relationship between STI and HIV, and numerous observational studies have demonstrated a 2-to-5-fold increased risk of HIV acquisition, especially with HSV-2/genital ulcers.<sup>25</sup> There is also evidence from quasi-experimental, cohort, and ecological data that STI control reduces HIV incidence.<sup>25</sup>

## When is a method “established”?

The recent WHO/UNAIDS/UNICEF report *Towards Universal Access* showed that even “proven” interventions like male circumcision are far from “established.”<sup>26</sup> For example, control of STIs and family planning are largely neglected as means of HIV prevention; and only 10 percent of adults had ever received voluntary counselling and testing. In addition, as described in the section *What “standard of prevention” is being provided in HIV prevention trials now?* on pages 24–25, what is currently being offered in HIV prevention trials is inconsistent, leaving a number of unanswered questions, including: How much risk reduction counselling should be provided and by whom? Should female condoms always be included, even if they are not available in the community? Can STI control in trial populations be improved through more consistently following the WHO recommendations, including treatment of HSV-2 and vaginal infections, periodic presumptive treatment in sex workers, improving partner notification and treatment, or vaccination against human papillomavirus?

## When should a new method be added to the standard HIV prevention package?

There are compelling arguments for offering new interventions such as male circumcision, acyclovir to treat herpes, and, if they are shown to be effective, oral PrEP or microbicides as part of the standard prevention package. But it is important to consider first how much can be achieved by improving the quality, intensity, and coverage of what is already available. There are many challenges to be addressed related to how currently available interventions are being provided in clinical trials. Prevention services and all aspects of clinical care need to be of high quality and offered consistently in order to be effective. In addition, some of what is currently being provided in prevention trials is not “proven,” and some of what is proven is provided neither

consistently nor correctly—either within or outside the clinical trials.

## Discussion

Several clinical researchers at the meeting noted that certain interventions provided to participants—such as STI diagnosis and treatment—should be considered part of clinical care and a health component of the trial, whether or not they are relevant for HIV prevention. At the same time, other critical issues associated with HIV risk are generally not included in the “standard of prevention” for example, addressing gender-based violence, or preventing and treating alcohol and substance abuse.

Many trial sites do offer these services to respond to participant needs and they are mentioned in the commentary of Guidance Point 13, but they are not generally considered part of the standard HIV prevention package.

The comprehensive review presented at the consultation and the ensuing discussion underscored the complexity of defining some of the terms in the UNAIDS/WHO guidance in order to determine when different HIV prevention technologies would meet the thresholds of evidence for being “proven” and “established” or, in the case of new technologies, being “scientifically validated.”

## Stakeholder perspectives

The 2007 UNAIDS/WHO guidance document recommends that agreements on when to include new prevention modalities should be negotiated among “all research stakeholders.” These stakeholders may have different perspectives on what “works” and what issues should be considered when determining whether to include a new product or innovation in the standard prevention package. A panel of diverse speakers was asked to comment on these issues. These individuals clearly do not represent all stakeholders, but their thoughtful and diverse experiences and perspectives are instructive for the challenges and opportunities for “stakeholder negotiation.”

### Normative agency

Most countries have normative agencies to set national policy. WHO’s guidance is very influential in the process that countries undertake to determine policy and practice at the national level. WHO has recently adopted a process to standardise how guidelines are produced. It specifies a grading process to evaluate the quality of evidence for developing guidelines based on study design and the strengths and limitations in the data. While this will help to ensure that guidelines are based on strong data, it may also limit flexibility and responsiveness.

### National regulatory agency

As presented from the perspective of the South Africa Medicines Control Council, the guiding principle of a national regulatory authority is first to “do no harm,” so safety concerns generally override considerations of product efficacy.

Approval of a new drug generally requires two randomised, controlled trials that reach statistical significance, but this requirement is not absolute and can, in some instances, be balanced against the burden of disease in the general population.

### Data safety and monitoring board (DSMB)

A DSMB’s primary responsibility is to the volunteers in the trial, ensuring that the risks and benefits to participants remain balanced in the face of any new evidence. A DSMB also tries to ensure that the trial will yield clear results. If a product shows benefit in another trial, the DSMB needs to consider whether it would be ethical to withhold this product from participants in the control arm. DSMBs are not responsible for considering any impact a decision about stopping or continuing a trial may have on another trial.

### Institutional review board (IRB)

In broad terms, IRBs look at the risk-to-benefit ratio of trial participation and what the investigators plan to do to minimise any potential harm to study volunteers. For the HIV prevention package, IRBs usually expect researchers to provide nationally approved tools that are already available, and specify the frequency, mode, and personnel responsible for delivering the service and the infrastructure used. Debate continues about whether a new method shown to be safe and effective must be included in the HIV prevention package if it has not been evaluated and implemented in the trial community.

## Advocates

Although advocates represent a range of perspectives and operate at different levels, most work to improve or accelerate access to new drugs and prevention tools, to ensure the rights of trial participants, and to articulate the broader implications of new prevention technologies (for example, the impact male circumcision may have for women). Advocates are key research stakeholders and, as such, should be included in all negotiations around trial implementation issues like standard of prevention.

## Investigators

Investigators face ongoing tension in meeting participants' needs. On one hand they may wish to provide a range of interventions and services, including new technologies, while on the other it may be better to focus on providing a reasonable core package consistently and well. Most investigators play multiple roles, including: serving as the public face of the trial available to diverse constituencies, from politicians to participants; being fluent in an enormous array of complex scientific, ethical, regulatory, and political issues; and managing the logistical, clinical, academic, budgetary, management, and scientific aspects of a trial. At many research sites, investigators are also responsible for multiple, different clinical trials, each of which may have different and, at times, divergent requirements. Against this backdrop, and working with limited resources, it may not be realistic to expect researchers to meet all of the expectations placed on them in the UNAIDS/WHO guidance document.

This tension was raised numerous times throughout the meeting, and it was illustrated clearly during two presentations. In one example, investigators from the Phambili HIV vaccine trial decided they should inform participants about male circumcision, based on the first male circumcision trial

results, and identify clinics that could provide male circumcision to all trial participants who requested this service. This was done in consultation with the community advisory board and the local ethics committee, and drew on local expertise to offer male circumcision at the vaccine trial site (possibly because one of the male circumcision trial sites was near to the vaccine site). These efforts were done at the initiative of the investigators, before national guidelines were developed.

Other researchers who attended the consultation argued for developing a core, evidence-based prevention package that is feasible to deliver. Currently there are no clear, specific international or national guidelines for the type of prevention package that must be provided in HIV prevention trials. In many countries, the national prevention policy is inconsistent with what is actually implemented in the country, as well as with what is provided at trial sites. While there would be some challenges, it should be possible to develop a core package that is standardised but also flexible enough to be adapted for different trials and trial settings, with clear justification in the protocol.

## Community

Most HIV prevention trials have developed and implemented extensive processes for community consultation, through meetings, information sharing, formal structures like community advisory boards, and other approaches. Most of these processes have been developed to “consult” with communities, with different approaches having advantages and drawbacks.

In proposing that solutions also be “negotiated” with key stakeholders, the 2007 UNAIDS/WHO guidance raises new challenges and opportunities for how these processes are structured. For example, several participants raised questions about whether “negotiation” is realistic given the knowledge and power differentials that often characterize the

relationships between a research enterprise and community advisory structures. One speaker presented a clear case for investing in building research literacy and capacity in communities where trials are ongoing or will take place, an approach that echoes earlier analyses. Other meeting participants suggested that the prevention research field explore multiple approaches to fulfill the guidelines' charge of consultation and negotiation while at the same time allowing for complex, sometimes technical decisions to be reached in a timely manner. While it may not be practical from a substantive or logistic standpoint to consult with all research stakeholders on all issues, it may

be more feasible and realistic to outline which organisations or entities among stakeholders are well placed to address different aspects of a trial.

It is important to consider the practical, implementation dimensions of an HIV prevention package. For example, should PrEP prove effective in one of the current clinical trials, individuals will likely access and start to use PrEP even before international guidelines or a national policy are put in place. This reality should inform decisions about whether to include it in the standard prevention package, to specify when trial participants should not use it, and to ask participants whether they have used it.

## Prevention trial realities

Trials of several biomedical HIV prevention methods are currently under way. As results emerge, researchers and normative agencies will need to grapple with the implications of results from these trials for other trials, including decisions about whether to continue, stop, or modify ongoing trials. Dr. Lynn Paxton of the CDC outlined the ethical, logistical, and scientific issues at the intersection of research and policy that the HIV prevention field will face as data from prevention trials become available in the near future. Dr. Paxton's presentation and the subsequent discussion, which focused especially on oral PrEP, underscored that these issues are not academic or theoretical.

At the time of the meeting, it was anticipated that interim results would be available for two PrEP trials: the Thai trial among injecting drug users was scheduled to meet six months after the Uganda consultation, and the iPREX trial was expected to report its first results in early 2010. Given that most PrEP trials involve different drug regimens that are being tested against different routes of transmission in different populations, it is unclear what implications, if any, the results of each PrEP trial will have for the other trials, or for public health policy and practice more broadly. Decision-making will not be a "one size fits all" approach and is likely to vary among and within countries. Decisions will need to be made in the absence of all the information we would like to have and as such will call for drawing on both science and interpretation, or what Dr. Paxton referred to as "art."

Investigators anticipating or learning results from another trial generally focus on these key questions: What are the implications for [our] trial? Does [our] trial need to be stopped? If not, will it continue with or without modifications? Answers

to these questions will be influenced by a range of factors, including: the strength of the evidence (both the magnitude of the effect seen and the statistical significance), the transmission route being studied, and the availability of results from other trials.

As outlined in the previous section, different actors will also have input into these decisions:

- **DSMBs** are charged with making clear recommendations about continuing or stopping a trial and play perhaps the clearest and most direct role.
- **Ethics committees** will review protocol amendments and assess compliance with the protocol. Based on this, they could also reassess a trial's balance of risks and benefits for the participants and determine that it is or is no longer ethical to continue a trial.
- **Governments**, through different regulatory and oversight mechanisms, could also determine whether a trial should stop or continue.
- **Communities**, through official structures like advisory boards or through activism, could raise concerns that could potentially stop a trial.
- **Individual participants** can freely decide to leave a trial at any time.

Results from current PrEP trials will emerge over several years, but there will be pressure for normative agencies to issue guidelines before all the results are in. Policymakers will need to balance the implications raised by a particular trial with the lack of the results of other, ongoing trials. This balance may vary based on the different real-life implications of a trial studying a new product (such as tenofovir gel) versus a product that is already marketed (such as oral tenofovir or



Truvada). For drugs already on the market, some people will begin to use them the day a positive finding is announced—whether or not the trial is directly relevant or there is any official guidance. For new drugs, the public will expect some kind of recommendation immediately, even though most regulatory agencies may require results from additional trials prior to approval and licensure. Finally, given the complex scale-up and access issues for many new products, it will likely take at least several years before such a product is available.

## Discussion

In the lively and wide-ranging discussion that followed Dr. Paxton's presentation, meeting participants voiced strong support for studies of PrEP currently being implemented to continue, whether or not there was an efficacy finding and assuming no safety concerns emerged in the completed trial. It is important to get a full picture of PrEP's effectiveness based on the different regimens, populations, and routes of transmission being studied in different trials. Policymaking and normative guidance will need to be informed by results from the diverse research portfolio. Most meeting participants also stated that they would consider the status of a trial (for example, whether is it new, ongoing, fully enrolled, etc.) in assessing whether it should continue or begin unchanged. Most also felt that starting a new trial would need to be more clearly justified (for example, examining safety and efficacy of PrEP in a new population or route of transmission) than allowing an ongoing trial to continue, where the process was

under way and significant resources had already been invested.

An example of this type of decision-making around trials and policy is the case of male circumcision in which policymakers determined that they wanted results from all three studies before making recommendations, so the two ongoing studies continued despite a strong positive result from the first trial. Preparation and consensus building started after the first trial, however, so that recommendations could be developed, issued, and acted upon as soon as possible after all trials were completed.

In short, most meeting participants felt that the burden should be on the research team to provide a clear scientific justification for why a trial should continue and to convey this information clearly to all stakeholders. It is especially important that trial participants understand the implications of any findings from other trials so they can make an informed decision about whether they wish to continue their ongoing participation in the study. It will also be critical to anticipate and to monitor how the reported results are interpreted and acted on by the community. Researchers can work with reporters and opinion leaders to clearly convey trial results—including any implications for the prevention research overall. Still, it is not always possible to influence how the media communicates trial findings. Therefore, all stakeholders need to monitor this carefully to ensure that the scientific findings are clearly presented and translated to key constituencies in a way that is accurate, understandable, and meaningful.

## What “standard of prevention” is being provided in HIV prevention trials now?

To further inform discussion about standards of prevention in HIV prevention trials, Dr. Samu Dube reported on research conducted by GCM to assess what is currently being provided at HIV prevention clinical trial sites, as well as the factors that influence the decisions and practice around what will be provided. GCM staff and consultants conducted an extensive mapping exercise of microbicide and diaphragm trial sites utilizing desk reviews, in-depth interviews, and site visits.<sup>27</sup> This analysis was supplemented by protocol reviews and interviews with investigators and staff from a representative sample of other HIV prevention trials in early 2009. These reviews looked at a range of prevention and care practices, including: the type and intensity of risk reduction counselling; condom promotion and provision; screening and care for STIs; provision of prevention services for partners; and cervical screening. The follow-up mapping exercise also looked at other prevention methods, including: male circumcision; clean needles, methadone maintenance, and drug treatment; and acyclovir for herpes suppression.

While some general categories such as condom promotion and risk reduction counselling were “standard,” there was a great deal of variation in the types and intensity of prevention services provided to participants in HIV prevention trials. For example, some studies offered risk reduction counselling monthly, while others did so quarterly or biannually. At most sites, participants could return between regular visits for additional counselling if they desired. Counselling staff—including counsellors, clinicians, social workers, field or outreach workers, peer educators, psychologists, and social scientists—at different trials and different study sites had

diverse training and backgrounds. The scope of the counselling also varied, from referral to a local voluntary counselling and testing clinic to individual counselling using a script, and even to messages and risk-reduction plans tailored to an individual client’s specific needs.

Similar variation was seen in provision of other prevention methods described above. While some of this variation was based on the particular product or method being studied and the study population, there was also variation among studies of similar products (vaginal microbicides, for example) and what was being provided at different sites within the same trial. The assessment found that this variation was due to a range of factors, including: local guidelines and standards; trial design considerations; the services and resources available in a local site setting; providers’ knowledge, comfort, training, and beliefs; and when the study started.

The “standard of prevention” between and within HIV prevention trials is anything but “standard,” and advocating for standardisation could have both benefits and drawbacks. For example, standardising what is offered through specifying the components in national prevention plans could help to protect trial participants through ensuring some degree of equity and fairness in what is provided in different trials in the same country. This approach could also benefit researchers by providing clear guidance on what is required and expected to meet a locally determined standard. A national standard would need to be adapted for different technologies and populations. However, such a standard may also make it more difficult for trials to innovate and be flexible in providing new and emerging technologies.

As new products and interventions become available, adding them to ongoing trials may require adjustments in the sample sizes, duration, and attendant costs of a trial, which will require flexibility among all stakeholders. Offering male circumcision as part of the prevention package in a trial that enrolls both men and women, for example, could create gender bias in the benefits of trial participation, and potentially influence endpoints and outcomes for participants enrolled in the study. Providing prevention methods that would not be widely available outside the trial may influence the applicability of any finding to the “real world.” There may be technical concerns as well. For example, introducing a drug like acyclovir would require sufficient data to allow researchers to ensure that any drug interaction would not influence the outcome of the trial, or that these drug interactions could at least

be measured accurately. The products or procedures themselves, as well as the larger numbers of participants that may be required to reach a given number of endpoints, could also make trials more expensive or even infeasible. Several meeting participants were skeptical that donors would be willing to extend the budgets and time frames for already expensive, complex, and long studies.

Finally, there has been relatively little effort to evaluate the efficacy of current prevention packages (such as condom counselling and provision, or STI testing and treatment) in HIV prevention trials. In general, the counselling and health care provided to trial participants is higher quality than what is available in the community. There is little evidence, however, as to whether these interventions are effective in reducing risk.

## Participatory exercises

### When should a new product be included in the prevention package?

Through a participatory exercise, meeting attendees were presented with different scenarios and asked to literally “vote with their feet” by moving around the room based on their reactions to different scenarios (see Box 2). The exercise was designed to elicit first reactions and impulses but people were encouraged to ask questions, to discuss the reasons for their responses, and to change their minds. Mirroring the actual decision-making processes that many stakeholders will be faced with, participants were required to “make decisions” even in the absence of complete information.

The exercise prompted a rich debate that highlighted the complex intersection among what would be ethically indicated, what would be desirable, and what would be feasible. In weighing these factors, some participants felt it would be important to distinguish between whether the prevention package was meant to primarily meet the ethical obligation to *minimise risks* of study participants or the obligation to *maximise benefits* to study participants, noting that this might lead to weighting the factors differently.

### Providing access to HIV prevention in a research setting

Meeting participants were divided into small groups designed to include individuals with different backgrounds and perspectives. The groups were presented with a series of hypothetical “findings” from ongoing PrEP trials, then asked to identify the criteria they would use to decide whether to stop or modify existing PrEP trials. This discussion elicited many of the criteria that were later debated and incorporated into the meeting’s recommendations, including:

- Whether the trial was conducted in a comparable population.
- Whether it was the same drug being tested (Truvada or tenofovir).
- Whether the new risk-reduction intervention would interfere with the trial’s ability to isolate the effect of the test product (such as an anti-retroviral [ARV]–based topical microbicide).

Participants agreed that the trial DSMBs and IRBs would need to be contacted, with the trial brochure amended and trial participants informed of how the results may affect the trial they were enrolled in. Finally, DSMBs might need to look at their trial data more frequently to assess whether any changes would be indicated in the thresholds for stopping the trial for benefit.

## When should a new product be included in the prevention package?

### Scenario 1

Starting with an example based on a trial of PRO 2000, a candidate microbicide gel, trial participants were asked to “decide” what impact results from that trial might have on other trials under a series of hypothetical situations:

- If the HPTN trial results showing a 30 percent reduction in risk had been statistically significant, should PRO 2000 be included as part of the prevention package in a future HIV prevention efficacy trial enrolling women in Tanzania?
- If the MDP 301 trial results had indicated that PRO 2000 reduced risk by 40 percent, meaning there were now two trials showing partial efficacy, should it have become part of the prevention package?
- If the product was partially protective against HIV as outlined above, but had not been licenced anywhere because of debate about the utility of a product with moderate efficacy, should it become part of the prevention package?
- If it were licenced in South Africa, but nowhere else in Africa, should it become part of the prevention package?
- If it were endorsed by WHO as a method for women who could not persuade their partners to use condoms, but had not been licenced in the country where the trial is taking place, should it become part of the prevention package?
- If two trials had shown partial efficacy for PRO 2000 but there was residual concern about safety of the product at higher frequency of use, should it become part of the prevention package?
- If PRO 2000 were approved for use in the trial country (Tanzania), but was only available in a few settings where introductory studies were being conducted (not including the community where the trial is being planned), should it become part of the prevention package?

### Scenario 2

A second brief scenario used examples related to male circumcision as a risk-reduction strategy for the male partners of women enrolled in a microbicide trial:

- In a future trial of dapivirine gel (a microbicide candidate containing an ARV drug), would it be obligatory to counsel participants (all women) on the risk-reduction benefits of male circumcision? Should circumcision be offered to the male partners of the women enrolled in the trial?
- Would this be different if it were a trial enrolling men?

## Key issues for trials and beyond

Throughout the meeting, discussion and debate covered a set of core issues related to developing and implementing a standard of prevention, as summarized below. At the same time, providing access to care or new products in a trial site also prompted debate about a number of key issues, including sustainability, the jurisdiction of national and local authorities, the meaning of access, undue inducement, and feasibility. During this lively discussion, participants were encouraged to think about the practical implications of the ethical frameworks and arguments presented. A number of issues emerged—sustainability, authority and responsibility, and isolating the effect—that did not derive from ethical principles directly.

### Innovation and sustainability

Clinical trial sites have resources that may not be available elsewhere in a community and as such have an opportunity to spearhead innovation in providing access to new products and interventions. A number of meeting participants, however, felt that trials should only be required to provide products and services that were already approved by local or national authorities, even if they were not available in the specific trial setting. Others stressed that trials can provide an important opportunity to expand the scope of what is available in a country or community, as well as helping to train providers and to allow users to gain understanding and experience by serving as a de facto demonstration project for new product introduction.

Some participants at the meeting also felt that trials should not introduce and provide services and products that will not be sustainable in the trial setting after the completion of the trial. Others felt

that sustainability, while an important consideration, may be an unrealistic expectation for a discrete research project. Requiring “sustainability” may ironically hamper aspirations about what is possible and curtail providing new methods, and several examples were provided about interventions that would not have been considered “sustainable” even a short time ago (for example ARV therapy and nevirapine for prevention of maternal to child transmission). In this context it can be helpful to emphasize one of the positive benefits of research, namely that it can improve and drive or ‘ratchet up’ the standard of care available in many settings.<sup>28</sup> For example, in many settings early roll-out of ARV therapy under the US President’s Emergency Plan for AIDS Relief and Global Fund programs was built around research sites that already had been providing HIV treatment.

Some meeting participants felt that responsibility for ensuring sustainability, while desirable, is beyond the scope of a research effort and rests more with national governments and public health systems. Several went further, underscoring that *no* entity can be held responsible for “ensuring” sustainability; doing so is effectively impossible in that it would require predicting accurately an unknowable future.

### New products versus established products

In negotiating criteria for a “state-of-the-art” prevention package, it is important to recognise the differences in making available a new product (such as novel microbicides or vaccines) versus using existing products for a new indication (such as tenofovir or Truvada for PrEP). A host of issues, including regulatory review

and licensure, international guidelines, national policy, manufacturing, and logistics, will likely be more complex and time consuming for new products. It will likely take several years after demonstrating efficacy before a new product can be commercialized, registered, and manufactured at scale. This means that a new product would not be available for introduction or for inclusion in the prevention package of a clinical trial for several years.

### **Undue inducement**

One concern that emerged derives directly from the field of research ethics: namely whether offering trial participants access to high quality products or services that are not otherwise available or affordable in the trial community would constitute “undue inducement” for people to participate in the trial. The CIOMS guidelines define undue inducement as:

“Payment in money or in kind to research subjects should not be so large as to persuade them to take undue risks or volunteer against their better judgment. Payments or rewards that undermine a person’s capacity to exercise free choice invalidate consent.”<sup>18</sup>

It may depend on the demand for a particular method in the community, whether participating in the trial would be the only way to access that service or technology, as well as the relative monetary value of the service. One person stressed, for example, that if the cost of medical male circumcision provided or paid for by the trial was US\$30 it would not constitute an undue inducement, but if the cost of the procedure was US\$500 it might. From an ethics perspective, the term and concept of “undue inducement” is often over used or misused in discussions of trial ethics. People make their own decisions about risks and benefits in assessing whether to enter trials, so an offer that might be an “undue inducement” to one participant might not

be so for another participant. In general, however, because there is not an enormous amount of risk associated with participating in HIV prevention trials, offering real benefits to participants is unlikely to constitute an “undue inducement.”

### **“Providing” a service**

Another debate among meeting participants concerned what is and what should be meant by “providing” a product or service to trial participants. Would this mean, for example, that trials would need to provide all products and services directly at the trial site, or could the trial refer participants to other services in the community? In the case of referrals, debate centred on how “active” the referrals would need to be. Examples of this range of activities include: Would the trial need to enter into a contract with the referral site? Would it need to pay for the service? Would it need to help with appointments, to provide transportation, or to have staff accompany participants to the service site to facilitate the process? The UNAIDS/WHO guidance document advises that when referral mechanisms are established, follow-up processes should be instituted to ensure quality case management services. In some cases strengthening existing services to accommodate referrals from a trial may contribute to sustainability and availability of that service in the larger community.

### **Meeting research needs and objectives**

In some situations it simply may not be practical to include new prevention technologies as part of the standard of prevention due to the particular products being tested and their mechanisms of action. For example, with microbicides formulated as gels, it may not be feasible to expect trial participants to apply two gels—the test product or placebo plus a proven microbicide. It would not be practical to expect this of participants nor

would it be scientifically feasible to isolate the effect of the test product. Depending on how closely the product's formulation matched another test product, it may be possible to use it as a comparator in a non-inferiority trial. Similarly, providing an ARV-based product (like PrEP) as part of the prevention package in a trial of another ARV-based product (such as a microbicide containing tenofovir) may make it scientifically impossible to tease out the effects of either product. Finally, at some point a “comprehensive” prevention package—with repeated counselling, testing, additional products, and so forth—may in fact become burdensome for the very participants it is designed to benefit.

It is also critical to consider the capacity of research sites that are already trying to implement extremely complex trials, and whether requiring them to provide diverse additional prevention services like male circumcision or a new and unfamiliar product would be feasible logistically or financially. Requiring too much of a trial could jeopardize the trial's ability to finance and conduct research by making trials too expensive or unwieldy.

### **Developing a core prevention package**

A number of people at the meeting supported the notion of developing a core HIV prevention package that was consistent and practical, yet also adaptable and flexible enough to allow each trial and trial site to examine, to modify (with clear justification), and to apply the standard. Others were concerned that such a core package would stifle innovation and responsiveness to local needs and priorities. Such a core package may also exacerbate challenges of implementing multi-site trials. Negotiating operational issues would be especially complex in multi-site trials, where available services may differ and the stakeholder process may lead to different recommendations and expectations about the type of prevention package that should be provided.

### **Authority and responsibility**

Ethical principles are just one factor guiding decisions and actions around design and implementation of clinical trials. Indeed laws, policies, customs, and other factors may influence “ethical” debates, and at times may even preclude doing that which seems “ethical.” As the process of designing and conducting research trials is currently configured, the ethics committee and the government are the only institutions that have the authority to formally approve protocols or protocol amendments. It is critical that these oversight bodies, and the people on them, maintain their autonomy and independence from the trial and the study sponsors. At the same time, engaging government and other policymakers from the outset is critical given their multiple roles in overseeing research, in providing the public health services where trial participants may be referred, and in determining whether new prevention modalities are ultimately approved and made available.

### **Trial ethics in context**

Ethical obligations to trial participants need to be viewed within the broader context of care and treatment programs, particularly around the availability of ARV therapy in the trial community. There is growing concern that the supply of ARV drugs in many hard-hit communities is becoming limited, and so may in effect begin to be rationed. If PrEP is proven to be efficacious, what would be the “ethical” implications of requiring “state-of-the-art” prevention for HIV-negative trial participants when there may not be enough ARV drugs to treat people who are already sick? It is difficult to imagine that otherwise healthy participants in an HIV prevention trial would—or should—be prioritised to receive limited drugs as part of a standard prevention package over people with HIV who need treatment. Several meeting participants noted that



it is important for everyone working on HIV prevention to continue to advocate for increased funding and resources for HIV treatment programs. However, it seems increasingly likely that the need for ARVs will outstrip the supply, particularly given the current economic climate, and that it is unrealistic to expect unlimited availability of drugs or funds for treatment or for prevention research.

### **Individual rights and public health needs**

A fundamental dilemma that HIV prevention researchers and advocates face is that the ethical frameworks used for ensuring that clinical trials are designed and conducted appropriately are oriented toward protecting individual rights and autonomy. In HIV prevention trials, one manifestation of this is the well-recognised ‘researchers’ dilemma’ of, on the one hand, striving to minimise participant risk by providing access to effective prevention modalities and, on the other hand, needing to see endpoints in order to be able to assess whether a novel prevention modality is effective in reducing risk of HIV infection. Several people at the meeting argued that it is also important for the ethics field to develop an “ethics of public health,” which would balance the considerations

of greater societal benefit with individual rights and health. Such a framework might, for example, allow balancing the responsibilities to trial participants with the urgent need that people outside the trials have for new HIV prevention methods and the importance of moving HIV prevention research forward. While there is some risk that this could be perceived as a way of diminishing researcher responsibility toward individual study volunteers, a number of meeting participants felt that developing such a framework through rigorous ethical reasoning is an urgent priority and committed themselves to taking this work forward.

### **Access and sustainability of trial products**

While not directly related to standards of prevention, a number of participants, particularly investigators and researchers, voiced concern about whether participants, communities, and trial country governments have realistic expectations with respect to access and sustainable provision of trial products that are shown to be effective. While many stakeholders focus these expectations on researchers, long-term responsibility for access to new health innovations must be shared by the government and public health sectors.<sup>b</sup>

<sup>b</sup> While it was not discussed extensively at the meeting, the UNAIDS/WHO Guidance Point 19 clearly states: “During the initial stages of development of a biomedical HIV prevention trial, trial sponsors and countries should agree on responsibilities and plans to make available as soon as possible any biomedical HIV preventive intervention demonstrated to be safe and effective, along with other knowledge and benefits helping to strengthen HIV prevention, to all participants in the trials in which it was tested, as well as to other populations at higher risk of HIV exposure in the country.”

## Points of agreement and disagreement

The rich and varied presentations and debates at the meeting culminated in a facilitated discussion aimed at developing a set of decision-making criteria. These criteria are intended to guide consultation among stakeholders as to whether and when to add prevention methods to the prevention package in ongoing and future trials. While participants were able to reach agreement on a number of issues, many questions remained unresolved. This reflects the ongoing challenge of developing broad principles that can inform and be applied across different types of trials, diverse settings, and unanticipated scientific developments. After lively debate and the expression of a range of views on how different factors should be prioritised, the group agreed on the following points:

1. If an international normative body and/or a national policymaking process recommended the use of a new method or strategy for HIV prevention for the population group enrolled in the trial, the presumption is that all trial participants should be ensured access to the method. Any departure from this recommendation must be clearly and persuasively justified on scientific<sup>c</sup> and ethical grounds in the study protocol.
2. In settings where high-quality prevention services are available in the community, it may be appropriate to provide access to new prevention tools either by direct provision at the trial site or by referral. If participants receive access to new prevention tools via

referral, researchers and trial sponsors must use a system of active referrals to monitor access and to ensure quality care.

3. It is the responsibility of the researchers and trial sponsors to ensure that new HIV prevention tools included as part of the standard prevention package are made available at no additional cost to study participants.

Meeting participants also grappled with the more complex question of how to decide whether to make a particular prevention method available in the absence of clear recommendations from normative agencies. The group developed the following list of criteria that stakeholders should consider in deciding when to add a new HIV prevention tool to the standard prevention package in a trial:<sup>d</sup>

1. What is the weight of evidence for estimates of efficacy or effectiveness of the new HIV prevention tool, including: the point estimate and confidence limits for any estimate of effect; the consistency of the data across different trial sites and in different study populations; and the number and type of clinical trials demonstrating an effect (particularly since a single trial is seldom accepted as establishing “proof”)?
2. Has the efficacy or effectiveness of the new HIV prevention tool been demonstrated in a comparable<sup>e</sup> population and for a comparable route of transmission?

c For example, trial endpoints could not be reliably reached.

d While cost was not addressed directly at the consultation, researchers and donor agencies will need to consider it as an additional factor when deciding to add a new prevention technology to the standard prevention package.

e For example, even if PrEP is found to be safe and effective in the current Phase 3 trial of injection drug users in Thailand, this doesn't mean that the same PrEP regimen will be equally safe and effective for heterosexually exposed women in Zambia.

3. Are there residual safety concerns or other unanswered questions that could call into question the appropriateness of the new HIV prevention tool for the trial participants (e.g., antagonistic interactions with other components of the prevention package, concerns about frequency or duration of use, or cultural practices that could affect safety)?
4. Have the safety and efficacy or effectiveness data been reviewed and accepted by experts other than the trial investigators?
5. Is there general agreement in the public health community that the new HIV prevention tool would likely provide some protective benefit for the population enrolled in the trial?
6. Will it be feasible to provide trial participants with the new HIV prevention tool given local availability and accessibility, manufacturing and importation restrictions, or other relevant factors?
7. Will adding the new method undermine the trial's ability to isolate the efficacy of the HIV modality being tested?

While it is difficult if not impossible to proscribe what priority these factors should be assigned for a particular trial, all of them should be explicitly examined and weighed as part of a stakeholder decision-making process.

### Additional points of agreement

Meeting participants identified a number of other points of agreement relevant to establishing the prevention package for biomedical HIV prevention trials including the following:

1. All HIV prevention trial participants should be guaranteed access to free

treatment for curable STIs as part of the standard prevention package.

2. In the absence of clear safety or futility concerns raised by relevant stakeholders—including ethics committees, DSMBs, investigators, trial sponsors, or study participants—existing PrEP trials should be allowed to continue to completion, even if one or more of the current trials demonstrates effectiveness.<sup>f</sup> From a scientific perspective, one trial seldom is sufficient to demonstrate safety and effectiveness for all at-risk populations and all routes of exposure, particularly given the diverse populations, settings, and regimens being studied across these trials. Regulatory agencies may also require additional studies for licensure and approval of PrEP as a new HIV prevention method. Participants in ongoing PrEP trials, however, should be informed of the results of completed studies.
3. Because of potential drug-drug interactions, PrEP or ARV-based microbicides should not be included in the standard prevention package for trials in other ARV-based prevention strategies until concerns about safety, toxicity, and other possible interactions are addressed adequately.<sup>g</sup>
4. If a new, proven HIV prevention tool is excluded from the standard prevention package of an ongoing or planned trial, researchers and trial sponsors, in collaboration with national government representatives, community advocates, and other stakeholders, should develop a carefully thought-out and well-executed communication strategy to explain the clinical, scientific, or ethical justification for not adding the new prevention tool to the standard prevention package.

<sup>f</sup> This recommendation refers specifically to the seven existing PrEP trials that are or are likely to be in the field at the time of publication, and should not be considered to be a blanket statement about all trials.

<sup>g</sup> Besides safety concerns, using PrEP in a trial of an ARV-based microbicide (or vice versa) may make it difficult to isolate the effect of the drug-based intervention under study.

## Need for additional guidelines and criteria

Despite general agreement on the guidelines identified above, considerable disagreement and debate remained around a number of key issues, including responsibility and sustainability. For example, participants disagreed on how important endorsement by normative bodies or the potential for “sustainability” of a new prevention tool in the community should be in weighing whether to include new prevention tools.

As described earlier in this report, some meeting participants felt that new methods should not be provided in a trial until they have been endorsed by normative agencies for that same population. Several also felt that a new method should not be provided unless it is approved by national regulatory authorities, while some took this point further to state that the new method would need to be included in the national prevention policy of the country where the trial site is located. Some meeting participants felt that research teams should not provide HIV prevention tools that are not widely available in the community or country where the trial is taking place.

Others argued that with its greater resources, research can provide an opportunity to innovate through introducing new prevention methods. Trial volunteers would benefit from access to new methods, and such efforts may also allow providers and programs to gain experience with new tools and interventions. While most agreed that “sustainability” should be the aspiration of all services provided in research, many dismissed it as too high a burden to place on research, noting that no entity—public, private, national, or international—can effectively ensure sustainability of any program and that requiring this of researchers and sponsors is simply too high a bar. Furthermore,

many participants underscored that service provision and sustainability are ultimately the responsibility of governments, not research teams or sites. While it cannot be guaranteed, trials often do improve the standard of care in communities, for example in vaccine trial sites that were among the first to provide ARV therapy in Africa.

### Consultation and negotiation

Given these real differences, a range of other outstanding issues, and the likelihood that new challenges will continue to emerge as research moves forward, it is important to continue a process of debate and consensus building. The UNAIDS/WHO guidance document states that determining when to incorporate new prevention tools and related issues should be resolved through consultation and negotiation among all research stakeholders, including communities. While many trials and trial networks have structures like community advisory boards in place, this process of negotiating when to add new prevention strategies to a trial protocol is well beyond what most of them are charged with. Implementing such a process may require new mechanisms and mandates to define and engage “research stakeholders.” This diverse group may include host community members, advocates and activists, ethics committees, donors and trial sponsors, investigators, national regulators and policymakers, treatment and prevention programs, and people living with HIV.

Negotiating among such a diverse group will require joint capacity building to develop a common understanding of the scientific, ethical, practical, and political dimensions and implications of

such decisions. It will be important to develop a clear process of consultation and negotiation, approaches to ensuring fairness and transparency, criteria for determining what organisations and individuals to engage on which decisions, and, critically, how to resolve inevitable conflicts. A critical component of this work must be to evaluate and share experiences, and to constructively resolve problems and conflicts.

### **Balancing individual rights with public health needs**

While the HIV prevention research field continues to grapple with appropriate standards of prevention for trial participants, it needs also to consider new approaches to balance the needs and rights of individuals enrolled in trials with the pressing need for new HIV prevention modalities. Despite the rich and complex discussions and debates, the consultation deliberations did not really grapple with two of the key questions posed at the outset of the consultation:

- What impact will including additional prevention modalities have on the ability of future trials to evaluate the efficacy of future HIV prevention tools?
- Should the continued addition of partially effective tools to the standard prevention package make it otherwise impossible to test new technologies, would the urgent public need for additional HIV prevention technologies ever justify reconsidering the level and type of prevention modalities provided to trial participants?

While the need to answer these questions can seem very far off, they are among the most pressing issues facing the HIV prevention research field. A framework of “public health ethics” will form a critical underpinning for addressing these questions, and several participants at the consultation pledged to take that work forward. It will be important to hone these questions and work toward developing answers that acknowledge all the associated complexity: ethical, scientific, individual, and political.

## Looking ahead

Ironically, any success in the long search for new prevention technologies will make subsequent HIV prevention trials more complex. It will then become even more difficult to identify additional prevention technologies. The Uganda consultation described here was an initial step in articulating issues, developing points of agreement, and identifying outstanding topics for debate in this charged and difficult arena. It will be important for this discussion to continue and to evolve at several levels. First, the prevention research field should continue to widen the debate and discussion and, as needed, adapt and add to the criteria for decision-making and points of agreement outlined above among different constituencies and in different venues. This debate will also need to be informed by and accommodate new data and information as they emerge from trials. Concrete decision-making

processes for trials and trial communities will need to be developed, implemented, evaluated, and adapted as outlined above. All of this will require investment from all stakeholders, many of whom are already overburdened.

Finally, the field will need to invest in the intellectual and political work to develop new frameworks for considering the needs and rights of individuals in trials within the overarching global need for new prevention technologies. While the UNAIDS/WHO guidance appropriately frames the decisions around standard of prevention and other aspects of trial design as ethical issues, they are also scientific, practical, and political. The prevention research field and its allies must continue to balance the ethical and personal commitments to trial participants with the urgent need for new prevention technologies.

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