HHS Public Access

Author manuscript

Bioethics. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Bioethics. 2015 June ; 29(5): 316–323. doi:10.1111/bioe.12113.

Clinical Trial Design for HIV Prevention Research: Determining Standards of Prevention

Liza Dawson and

is Team Leader for Research Ethics, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health. She has worked in bioethics and human research protection at NIH for the past 11 years, focusing primarily on clinical trials and international research. Prior to that, worked at the Bioethics Institute of Johns Hopkins University School of Public Health and was a consultant to the National Bioethics Advisory Commission

Sheryl Zwerski

MSN, CRNP is the Acting Director of the Prevention Sciences Program at the Division of AIDS at the National Institute of Allergy and Infectious Diseases (NIAID). She has worked in HIV research and care since 1987 with the last ten years being spent in HIV prevention research. Prior to her work at NIAID she was a nurse practitioner/clinician/associate investigator with the pediatric branch at the National Cancer Institute and before that in the pediatric immunology division at the University of Florida

Abstract

This paper seeks to advance ethical dialogue on choosing standards of prevention in clinical trials testing improved biomedical prevention methods for HIV. The stakes in this area of research are high, given the continued high rates of infection in many countries and the budget limitations that have constrained efforts to expand treatment for all who are currently HIV-infected. New prevention methods are still needed; at the same time, some existing prevention and treatment interventions have been proven effective but are not yet widely available in the countries where they most urgently needed. The ethical tensions in this field of clinical research are well known and have been the subject of extensive debate. There is no single clinical trial design that can optimize all the ethically important goals and commitments involved in research. Several recent papers have described the current ethical difficulties in designing HIV prevention trials, especially in resource limited settings; however, there is no consensus on how to handle clinical trial design decisions, and existing international ethical guidelines offer conflicting advice. This paper acknowledges these deep ethical dilemmas and moves beyond a simple descriptive approach, to advance an organized method for considering what clinical trial designs will be ethically acceptable for HIV prevention trials, balancing the relevant criteria and providing justification for specific design decisions.

Corresponding Author: Liza Dawson, National Institutes of Health - NIAID/Division of AIDS, 5601 Fisher's Lane Room 9G59, Bethesda, MD 20892, USA, Tel: + 240-627-3210, dawsonl@niaid.nih.gov.

Keywords

standard of care; researchers' obligations; HIV prevention; clinical trials; biomedical research; low and middle income countries

Recent advances in HIV prevention research raise questions about designing future prevention trials. Specifically, with new biomedical HIV prevention methods validated, questions arise about possible changes to comparator groups or background prevention packages in clinical trials. The implications of these changes are significant. Standard of prevention, like standard of care, is an important design consideration in clinical trials, since it affects participant welfare, scientific validity and efficiency of the trial, framing of the research question, and relevance for health policy decision-making. In this paper, we outline the main ethical and scientific considerations for decision-making regarding standards of prevention.

There are two ways of incorporating prevention interventions in a clinical trial: providing the same interventions to both/all groups in the trial as a background package, or using a known effective intervention in an active control group, rather than a placebo or inert control. These two ways are not mutually exclusive; a trial could include a background prevention package in, for example, two study groups, plus interventions A and B (both active) in the two study arms.

Questions about standards of prevention for trial participants in HIV clinical trials recall previous debates about standards of care. In 1997, critics of HIV prevention of maternal to child transmission (PMTCT) trials claimed that trial participants had been inadequately protected because best standard of care had not been provided in the control group. Defenders of the trials cited concerns about the need for studies to be relevant to local conditions, arguing that testing less intensive methods against placebo would yield results that were more feasible to implement than best standard of care. This dilemma involved a clash of two important ethical commitments: concern for study participant welfare, and concern about utility of trial results.

The standard of care dilemma is emerging again in the context of HIV prevention trials. Until now, trials have largely been designed with active product(s) versus placebo(s) on top of a standard background prevention package provided to all trial participants, usually consisting of risk reduction counseling, condoms, and basic primary care services such as STI diagnosis and treatment.

Now new biomedical prevention products such as pre-exposure prophylaxis (PrEP) have been proven effective in some populations, prompting questions about incorporation of these products into trials, either as background prevention or active control arms. Box 1 outlines the principle issues at stake when additional prevention methods are incorporated into trials: study design, welfare of trial participants, feasibility, study costs, and utility of trial results. And while there are possible benefits to trial participants from additional prevention interventions, there are also worries about increases in risk-taking behavior; barriers to

adherence; inequities within groups or communities; and “undue inducement” to participate in trials.

Stakeholder discussions have addressed the question of level or type of prevention in HIV clinical trials[1] and have outlined areas of consensus or disagreement, as shown in Table 1. There are certain basic standards for HIV prevention trials, for example inclusion of a basic prevention package for all trial participants involving counseling and provision of condoms, that arguably, all stakeholders would agree to[2]. But beyond these basic standards, consensus breaks down.

There is no agreement about best conceptual approach to determine researchers' obligations in addressing the standard of prevention problem. Debates continue about whether researchers should provide prevention modalities to trial participants that are not locally available. Most design decisions affect one or more of four key aspects: participant and community welfare, scientific viability, efficiency, and usefulness of results. (See Box 1). Often, a study design that optimizes one aspect will adversely affect another. In Table 2 we outline some examples of study design choices and how they affect these four parameters, which we discuss further below.

Welfare of Study Participants and Communities

A number of arguments have been advanced for providing a higher standard of prevention to trial participants than what is locally available. We note that while there is obviously potential for direct benefit to participants from provision of prevention modalities, the implications for trial relevance, efficiency and scientific validity may be either positive or negative, as shown in Table 2.

Some commentators believe researchers have a duty of rescue, or duty of beneficence, when confronted with unmet medical needs of trial participants, especially in Low and Middle Income Countries (LMIC)[3], duties that stem from the ability to assist others in need, regardless of a prior relationship. The challenge of general obligations is that they become broad and overwhelming, with no clear way to distinguish which individuals must be helped amongst the many in need. Others advocate for benefits to research participants as a form of gratitude for their participation in research[4]. On this view, study participants' contribution to society should stimulate reciprocity on the part of researchers by providing benefits to participants in a trial. A third view is that the researcher/participant relationship established in a clinical trial sets up a duty to provide benefits, including benefits above and beyond those available to others in the community[5].

These differing views raise fundamental questions about the nature of researchers' obligations to clinical trial participants. Some believe these obligations are based on clinicians' obligations to patients,[6] while others demur[7]. However even if there were consensus about basing researchers' clinical care obligations on those of health care providers, further questions emerge when health care providers in LMIC must implement public health programs that cannot provide expensive treatments. Many providers have been advocates for their communities in attempting to raise the standard of care for all[8]. However it is not clear that physicians would have obligations to give study participants benefit from

additional, higher standards of care that are not feasible or sustainable at the health system level. At issue is the complicated question of whether physicians must participate in actively rationing care or triaging resources for the neediest patients. In most health systems, resource allocation decisions are not made at the individual physician level. So even an argument that researchers' obligations mimic those of physicians does not provide a clear benchmark for standard of care in a clinical trial in settings where resources are constrained. In spite of these ambiguities, it is often the case that physician-researchers are among the strongest advocates for higher standards of care[9]—an illustrative example of physicians promoting maximum beneficence towards individual patients, in spite of health system constraints.

Layered on top of the conceptual difficulties regarding researchers' dual loyalties to study participants and to science, are a number of pragmatic concerns about adding new prevention methods to trials. Inclusion of additional prevention options in a clinical trial may create a mixture of harms and benefits with unknown net effect, or differential effects on different individuals. For example, participants may not be able to effectively use multiple prevention methods in combination; or use of one method may decrease motivation to use others. Formative research on use of combinations of prevention products is underway, and the ultimate feasibility and acceptability of using combination packages must be carefully studied in clinical trials and demonstration projects. It is reasonable to require some evidence from these kinds of studies prior to including combination packages in efficacy clinical trials.

Other concerns about standards of prevention relate to community impact. Some commentators have expressed concern about the creation of inequalities of access to new prevention tools not locally available when clinical trial participants gain access through a trial, and about the problem of sustainability when the trial ends.[10] These questions about feasibility of local implementation overlap with worries about the usefulness of trial results —if clinical trials test modalities that are not in local use, will results lack applicability to the local setting? It is often the case that immediate availability to trial communities is out of reach, but longer-term, broader access may be possible when policy and funding plans have been developed. Further efforts are needed on a broad scale to link successful research trials to program implementation.[11] It is conceivable that specific trials can be used as a launching pad for broader implementation. However, the conduct of the trial itself is unlikely to be sufficient to address all the regulatory, manufacturing, policy and funding issues at stake in rolling out a new intervention.[12]

Ultimately, in the context of HIV prevention trials, consideration should be given to providing higher levels of direct benefits in the trial, even if these benefits are not available to everyone in the community. Providing benefits in a trial provides a compensatory mechanism to balance risks or burdens. However, provision of benefits often leads to concerns about undue inducement to participate.

Substantial debates have taken place in the bioethics literature regarding undue inducement, reflecting disagreement about how the term should be defined and whether or not it is truly ethically problematic. Certainly reasonable limits on risk in clinical trials must be set, to

reduce concerns that the attractiveness of research results in excessive exposure to risk. Given the realities that clinical trial participation is frequently attractive due to ancillary benefits, high quality care, and remuneration for study visits, it would be unrealistic to think that participants in resource-limited settings are enrolling solely out a desire to contribute to science. The question is whether enrollment in a trial based on the desire for tangible benefits is worrisome. A number of concerns have been raised: a) misconceptions about whether research is in fact beneficial; b) excessive risk-taking in research out of desire to obtain benefits; c) exploitation of participants' economic vulnerability; or d) low motivation to adhere to study procedures. In fact, when research does provide real benefits of enhanced medical care, and when risks are reasonably low, most of these concerns are alleviated; participants' interests are not being set back by their enrollment, and their desire to obtain benefits is rational choice, not a misconception. Importantly, if risks are high, this assessment may no longer hold. In regard to the attractiveness of trial benefits, low motivation for adherence may in fact be the most salient concern. Full consideration of this problem requires attention to social context and behavioral issues in the trial setting and better design of interventions to reduce adherence challenges.

In addition to individual benefits (or harms) of providing new prevention interventions, there is a broader level of community impact from the conduct of prevention trials. Negotiations and agreements about clinical trials, and ultimately how trials are conducted and reported, affect long term relationships among stakeholders and the potential harms of breakdown of trust and communication when these issues are not managed appropriately are manifold with potentially lasting and ultimately harmful effects for the communities involved.[13]

Scientific Validity

It is important to consider the implications of adding new prevention tools to the background prevention package versus creating new active control groups for clinical trials, as shown in Table 2. One central issue that affects active control trials (but not necessarily trials with additions to the background prevention packages) is reliability of trial results.[14] If an active comparator is believed effective but is ineffective in the trial, the trial can produce false positive results—which ultimately would affect whether trial results are suitable for regulatory or policy decision-making. The problem of adherence in HIV prevention trials can have a major effect on scientific viability. As recent VOICE study results demonstrate,[15] low adherence in a trial makes it impossible to measure effectiveness, and can lead to widely divergent results across studies. If trial participants in a study with an active control arm are non-adherent to the intervention in that arm, rendering it ineffective, researchers may falsely conclude that the experimental arm is effective, based on its having HIV incidence similar to that in the (now ineffective) comparison group.[16] The implications of false positive results are serious. Policy decisions and clinical guidelines based on false assumptions could waste valuable healthcare resources, lead to inadvertent risks of HIV exposure, and increase the human and economic costs of disease.

False negative trial results also have costs. If a trial of a product that is actually efficacious fails to show a positive result due to, for example, extremely low HIV incidence in the trial overall, then a potentially useful intervention might be abandoned. Such a result might occur

if a background prevention package provided to all trial participants was highly effective, reducing the HIV incidence below the level needed to achieve statistical power in the trial.

Another challenge to scientific validity occurs when trial participants receive several different interventions, for example, one biomedical product in the background prevention package and a different product in the experimental arm of the trial. It will be more difficult to determine the individual effects of each intervention in such a trial, and determining interactions between interventions would require larger sample sizes.

Behavioral factors can affect usage when several methods of prevention are offered simultaneously, as observed in the MIRA trial.[17] In that study, women in the intervention arm, who received diaphragms, were less likely to report condom use than women in the control arm. Given that the HIV incidence was similar in both arms, it is possible that the diaphragm provided protection that compensated for the lower condom use—but it is impossible to draw any reliable conclusions, due to the problems of unreliability of self-reporting, as well as non-randomized subgroups.

Efficiency

The second major concern in trials with active controls or trials with enhanced background prevention is the need for a very large sample size to achieve necessary statistical power, as noted in Table 2.[18] It may be possible to achieve reliable results, but due to the increased sample size, trials may be very lengthy and costly (see Table II). Active controlled trials also generally require larger sample sizes—and the more expensive the trial, the fewer additional trials will be conducted. Efficiency in conducting research takes on increasing ethical importance with finite research budgets and significant need to develop additional prevention methods to address unmet needs across populations at risk.

The need for efficiency is partly driven by concerns about distributive justice. If the tools and methods currently available are not accessible or feasible for groups at risk of HIV acquisition, failure to proceed expeditiously with further research leaves these groups unprotected. Many of these groups are already disadvantaged by social, institutional or economic processes that leave them marginalized or oppressed.[19] A failure to address their needs through additional prevention research exacerbates existing social inequalities and disparities in morbidity and mortality. For example, while PrEP showed outstanding success in several trials, none of the communities in LMIC are currently accessing PrEP, and due to adherence challenges for some populations, it is likely that more feasible and practical methods will be needed.[20]

In theory, concerns about efficiency could also be driven by industry sponsors' desire to conserve resources for their own purposes. However, the majority of HIV prevention trials are sponsored by publicly funded organizations or private philanthropic entities, and these sponsors' main concerns are the efficient and responsible use of resources to maximize public health, rather than financial gain.

In spite of the importance of efficiency, it is difficult to trade off efficiency of obtaining research results directly against trial participant benefits. Every research project, by

definition, involves uncertainties, including uncertainty about the degree to which that particular trial will contribute to future benefits for HIV prevention. Even if the incremental gains for future users were certain, a complex ethical calculus would be needed to weigh these benefits against benefits to current trial participants due to time delays and uneven implementation. And it is impossible to weigh future benefits in any quantitative sense. An efficiency argument alone is insufficient to justify a trial design where useful proven prevention methods are not provided to trial participants. Other efficiency measures that don't adversely affect participant welfare should still be a priority. This does not mean, however, that standards of prevention should necessarily include every prevention modality known to be effective: standards of public health relevance must still be met.

Usefulness of the Trial to Advance Health Policy Standards

Study findings can be useful in diverse ways: for informing further research or product development; for regulatory approval, and for policy changes at the public health level. The choice of comparator groups in clinical trials can affect the usefulness of study findings in all of these arenas.

For health policy decision-making, ideally a trial will test interventions or combinations that are relevant in the setting of the research.[21] All health research is geared toward ultimately improving health outcomes—but how to translate research into policy may be a matter of contentious debate. Research findings that can improve standards of care, within some measurable time frame, could provide tremendous benefit. But it can be difficult to predict if a new technology or standard can be implemented in the near or medium term. Costs, infrastructure demands, intellectual property, competing health concerns, and health budgets may all be uncertain. And there is no agreement about how immediate the application of study findings needs to be, to justify the trial. While reasonable availability has been considered a core principle by some, there are detractors who believe that stringent criteria for clinical trials will ultimately harm the low and middle income countries (LMIC) they were designed to protect.[22]

Despite the challenges of making accurate predictions, the relevance and social value of research is critical. Researchers and sponsors should try, to the extent possible, to anticipate the policy environment that will develop in the near and longer term future when designing trials. Conducting a trial that answers a question that is soon irrelevant wastes resources and betrays the trust of multiple research stakeholders. The central difficulty is making predictions about a future based on an array of present uncertainties.

Discussion

In sum, clinical trialists working in HIV prevention face dilemmas about the standard of prevention in new clinical trials. Incorporating more prevention methods into prevention packages, or into active control arms, may increase benefit to participants for the duration of the trial. However there may be drawbacks to this approach in terms of ability to answer the research questions, greater time to study completion, higher financial costs, and/or decreased relevance of results.

Ethical guidelines for clinical trials offer general guidance on control groups (CIOMS, Helsinki) but do not provide a mechanism for adjudicating the ethical tensions in trial design when considering benefits to participants, scientific soundness, and usefulness. HPTN Ethics Guidance and the UNAID Guidance on HIV Biomedical Prevention Trials provide different recommendations about criteria for standards of prevention. Most importantly, the underlying ethical tensions in determining the appropriate standard of prevention will need to be acknowledged and adjudicated on a case-by-case basis, as the field changes rapidly, and given the variability in different products, settings and populations,

More emphasis is needed on social value of research, not to place more restrictions on research, but to find ways to make research more efficient in producing knowledge for human health. Part of the larger problem underlying standards of care/standards of prevention is the uneven and slow progress of implementation of known effective interventions. So the larger solution to the standard of prevention problem entails better translation of research findings into programmatic changes. Pathways to this increased efficiency could include better selection of products for development, better use of targeted product profiles, more efficient coordination and partnerships amongst research organizations and implementers, increased resources for implementation studies, and organized social marketing and communication strategies to stimulate public uptake. In an ideal world, increasing the productivity and efficiency of research translation and implementation would leave fewer gaps to fill in the conduct of clinical trials—as well as reaping the public health benefits of research more quickly.

Finding a way Forward

Four activities are needed to address standard of prevention dilemmas. First, attention to long-term relationships in research is critical. Background conditions of injustice affect these relationships, and make it imperative to develop and maintain trust and collaborative partnerships. These relationships have instrumental value for stakeholders, in that they help research move forward productively, help communities advocate for their health needs, and help avoid conflicts which can have spillover effects on to other health related activities in the local setting. The relationships amongst key stakeholders provide the platform for discussion of the tradeoffs and challenges of choosing appropriate standards of prevention.

Second, robust processes for stakeholder engagement and communication on these issues are needed on an ongoing basis as trial questions and policy conditions change. Decisions about clinical trial design can affect both short term and long-term interests of individuals and communities where trials take place. There will never be a single uniform solution for standards of prevention, since all of the key parameters, participant welfare, scientific viability, and usefulness, can change over time and in different settings, as evidence grows and policies adapt. Therefore, transparency is key as new trials are developed and move forward. Adjudicating decisions about standards of prevention will require active participations of stakeholders from multiple perspectives and interests, with sufficient knowledge and experience with HIV prevention trials, to consider the balance of ethical, scientific and policy implications of a chosen trial design. Fortunately, extensive work on community engagement is already taking place.[23]

Third, more work needs to be done amongst key stakeholder groups (clinical trialists, mathematical modeling experts, health policy decision-makers, ethicists, and community representatives) in making better predictions about utility of different trial results in different scenarios. Researchers must continue to try and anticipate policy needs and changes to ensure relevance of trial results. In concert with these efforts, sustained attention is needed in regard to social and behavioral factors affecting acceptability, effectiveness and feasibility of prevention methods in populations at risk.

Fourth, more conceptual work is needed in defining researcher obligations in clinical research. More clarity is needed about how the demands of scientific rigor and usefulness in the policy arena can be ethically balanced with participant welfare concerns.

The standard of prevention in HIV clinical trials, like many controversial areas of HIV research, raises profound questions about ethical obligations for clinical care and research and about collective responses to global health inequalities. Further work in this area will not only bolster efforts to conduct ethically sound and useful HIV clinical trials; it will also contribute to broader discussions about the ethics of clinical research and attention to global health concerns.

References

1. Philpott S, Heise L, McGrory E, Paxton L, Hankins C. The challenge of defining standards of prevention in HIV prevention trials. J Med Ethics. 2011; 37(4):244–8. participants in the 2009 GCM/CDC/UNAIDSConsultation on Standards of Prevention in HIV Prevention Trials. 10.1136/jme.2010.037176 [PubMed: 21186207] Haire B, Folayan MO, Hankins C, et al. Ethical Considerations in Determining Standard of Prevention Packages for HIV Prevention Trials: Examining PrEP. Dev World Bioeth. 2013 Aug; 13(2):87–94.10.1111/dewb.12032 [PubMed: 23725227] Haire B, Kaldor J, Jordens CF. How good is “good enough”? The case for varying standards of evidence according to need for new interventions in HIV prevention. Am J Bioeth. 2012; 12(6):21–30.10.1080/15265161.2012.671887 [PubMed: 22650457]
2. Haire B, Folayan MO, Hankins C, et al *op cit*. note 1.
3. Hawkins, J. Exploitation and placebo controls. In: Hawkins, J.; Emanuel, EJ., editors. Exploitation in Developing Countries: The Ethics of Clinical Research. Princeton University Press; 2008.
4. National Bioethics Advisory Commission. Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Vol. I. Bethesda, MD; 2001.
5. Dickert N, Wendler D. Ancillary care obligations of medical researchers. JAMA. 2009; 302(4):424–8. [PubMed: 19622821]
6. Miller PB, Weijer C. Rehabilitating equipoise. Kennedy Institute of Ethics Journal. 2003 Jun; 12(2): 93–118. [PubMed: 14569997]
7. Miller FG, Brody H. A critique of clinical equipoise: Therapeutic misconception in the ethics of clinical trials. Hastings Center Report. 2003 May-Jun;33(3):19–28. [PubMed: 12854452]
8. Campbell, ME. XV International AIDS Conference. Bangkok: 2004. Preventing mother-to-child transmission of HIV in South Africa: a case study of civil advocacy and policy change. Abstract no. MoPeE4058
9. Dawson L, Klingman K, Marrazzo J. Addressing Standards of Care in Resource Limited Settings. J Acquir Immune Defic Syndr. Jan 1.2014 65(1)
10. Vallely A, Shagi C, Lees S. Microbicides Development Programme: Engaging the community in the standard of care debate in a vaginal microbicide trial in Mwanza, Tanzania. BMC Medical Ethics. 2009; 10:17.10.1186/1472-6939-10-17 [PubMed: 19814830]
11. Dawson et al *op cit*

12. Notably, agreements between non-profit research organizations and commercial entities are an example of a promising approach for moving positive clinical trial results in implementation mode.
13. Slevin, K.; Ukpong, M.; Heise, L. [accessed May 20th, 2014] Community engagement in HIV prevention trials: evolution of the field and opportunities for growth. Global Campaign for Microbicides. http://www.global-campaign.org/clientfiles/aids2031-ce.pdf
14. Grobler AC, Abdool Karim SS. Design challenges facing clinical trials of the effectiveness of new HIV-prevention technologies. AIDS. 2012; 26(5):529–32. [PubMed: 22210638]
15. Van der Straten A, Stadler J, Montgomery E, et al. Women's Experiences with Oral and Vaginal Pre-Exposure Prophylaxis: The VOICE-C Qualitative Study in Johannesburg, South Africa. PLoS One. 9(2):e89118.10.1371/journal.pone.0089118 [PubMed: 24586534]
16. Grobler and Karim, ibid.
17. Padian N, van der Straten A, Ramjee G, et al. Diaphragm and lubricant gel for prevention of HIV acquisition in southern African women: a randomized controlled trial. Lancet. 2007; 370:251–61. [PubMed: 17631387]
18. Padian N, McLoy SI, Balkus JE, et al. Weighing the gold in the gold standard: challenges in HIV prevention research. AIDS. 2010; 24:621–635. [PubMed: 20179575] Padian N, Buva A, Balkus J, et al. Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward. Lancet. 2008; 372:585–99. [PubMed: 18687456]
19. Baral S, Grosso A, Holland C, et al. The epidemiology of HIV among men who have sex with men in countries with generalized HIV epidemics. Curr Opin HIV AIDS. 2014; 9:156–167. [PubMed: 24445371]
20. Van der Straten, *op cit*.Van der Elst EM, Mbogua J, Operario D, et al. High Acceptability of HIV Pre-exposure Prophylaxis but Challenges I Adherence and Use: Qualitative Insights from a Phase I Trial of Intermittent and Daily PrEP in At-Risk Populations in Kenya. AIDS Behav. 2013; 17:2162–2172. [PubMed: 23080358]
21. Chang LW, Serwadda D, Quinn TC, et al. Combination implementation for HIV prevention: moving from clinical trial evidence to population-level effects. Lancet Inf Dis. 2013; 13(1):65–76.
22. Wolitz R, Emanuel E, Shah S. Rethinking the responsiveness requirement for international research. Lancet. 2009 Sep 5; 374(9692):847–9. [PubMed: 19733781]
23. Shagi C, Vallely A, Kasindi S, et al. A model for community representation and participation in HIV prevention trials among women who engage in transactional sex in Africa. AIDS Care. 20:9, 1039–1049.10.1080/09540120701842803Vallely et al *op cit*UNAIDS. [accessed May 20th 2014] Good participatory practice: Guidelines for biomedical HIV prevention trials. 2011. www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC1853_GPP_Guidelines_2011_en.pdfWhite R, Chileshe M, Dawson L, et al. Fostering community understanding of sufficient benefit and early stopping for a phase 2B HIV prevention clinical trial in Africa. Clin Trials. 2011; 8:103. [PubMed: 21335592]

Box I

Summary points

Four key parameters determine ethical acceptability of HIV standards of prevention in specific clinical trial design choices:

1. Scientific viability
2. Participant and community welfare
3. Trial efficiency
4. Trial usefulness for decision-maki

There are tradeoffs amongst these four parameters, and often, the four cannot all be optimized simultaneously. Some ethical aspects of each parameter are outlined below.

Parameter	Key ethical aspects	Interactions with other parameters
Scientific viability	Minimum standard must be met in all cases: trial as designed must be able to reliably answer the research question, given information available at the planning and initiation stages of the trial;	Attempting to address participant welfare and efficiency concerns have real potential to disrupt scientific viability; viability must be protected in any trial;
Participant and community welfare	Participant welfare should always be a priority, and formative research should be used whenever possible to predict effects of introducing new interventions on participants and their communities	Prevention packages cannot be designed solely to maximize trial efficiency if this comes at significant cost to participant welfare; however, public health relevance may provide some limit to the extent of benefits provided and may simultaneously promote efficiency
Efficiency	Trial efficiency is ethically important, because there are finite research resources and a large number of research questions which, if appropriately addressed, could have positive impacts on public health; trial efficiency should be a priority	Efficiency can be compromised for the sake of the other three parameters, as long as there is no alternative, more efficient approach
Usefulness of clinical trial findings	Trials at different stages of research are used for different types of decisions, from decision-making regarding next stages of investigation (phase I and II) to decisions about regulatory approval and policy implementation (phases III and IV). Planning should take account of the longest view possible about decision-making—looking down the road to the end of the trial and beyond, for what information is most relevant and most needed.	Greater emphasis is needed at all stages of research on attempts to predict what is most useful; this drives the ethical acceptability of research, since the overall objective is to improve human health and health care;

Table 1

Areas of consensus and lack of consensus

	Participant and community welfare	**Scientific viability**	**Efficiency**	**Usefulness**
Basic consensus standards	Participants and community ***no worse off*** (than baseline); no foreseeable, preventable increase in risk should be allowed	Trial meets ***statistical and scientific standards*** for answering primary research question		Trial addresses a research question which has some ***value for decision-making in one or more areas*** (for future research; regulatory; or policy)
Areas where there is no consensus	Including ***some or all best prevention methods when not locally available,*** which leads to issues surrounding sustainability in background package or in active trial arms		***How to use non-scientific criteria, such as cost, ease of enrollment, in trial design decisions*** especially when these issues affect participant welfare or usefulness of the trial	Whether there should be a requirement for ***responsiveness to host country priorities*** and/or ***reasonable availability*** of study products; and how immediate these benefits would need to be

Bioethics. Author manuscript; available in PMC 2016 June 01.

Table 2

Effects of different standards of prevention on key parameters

Standard of prevention:	Participant and community welfare	Scientific viability	Efficiency	Usefulness
Enhanced prevention package: adding new biomedical products or procedures that are not locally available	Positive: Potential direct benefits to participants; benefits to long-term stakeholder relationships amongst community, host country, researchers, research sponsors;	Positive: no bias created if same methods offered to both/all arms;	Positive: possibility of greater attractiveness of trial and faster enrollment	Positive: policy makers may be interested in combination approach; as new methods become more widely available, trial may predict "real world" outcomes; may contribute to driving towards improved standards of care (short or long term)
	Negative: increase inequity within study community; potential negative effects on adherence; potential diversion of products	Negative: potential for unintended adverse biological interactions with untested combinations of interventions;possible challenges of interpretation of effectiveness of individual prevention modalities	Negative: Possibility of increased trial costs/time due to lower HIV incidence across all arms of trial	Negative: Regulators may only issue approval for products when used in combination; possible decreased policy relevance (policy makers may not want to implement entire package); policy makers may be interested in results of single method used alone;
Active control arm: using biomedical prevention method as active control	Positive: Potential for:direct benefits to participants;	Positive:	Positive:	Positive: hold new products to high standard; (match or beat control); see results of two methods in same trial to base future policy decision-making on comparable data from same population;
	Negative: increase inequity within study community; potential diversion of products; more difficult to justify randomization to experimental arm with a known effective control arm	Negative: Possible false positive results in non-inferiority designs; cannot detect efficacy of products less efficacious than control arm	Negative: increase in sample size to detect difference between arms and establish non-inferiority or superiority; increased trial size, duration and cost;	Negative: Regulators may not accept trial design for marketing approval; policy decisions based on false positive result could waste health funds, increase risks; products with lower efficacy than control, but still with public health value (for example more feasible or acceptable), may not be considered for implementation