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Fostering Community Understanding of Sufficient Benefit and Early Stopping for a Phase 2B HIV Prevention Clinical Trial in Africa

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Abstract

Background—Most trials of interventions are designed to address the traditional null hypothesis of no benefit. VOICE, a phase 2B HIV prevention trial funded by NIH and conducted in Africa, is designed to assess if the intervention will prevent a substantial fraction of infections. Planned interim analysis may provide conclusive evidence against the traditional null hypothesis without establishing substantial benefit. At this interim point, the Data and Safety Monitoring Board would then face the dilemma of knowing the product has some positive effect, but perhaps not as great an effect as the protocol has declared necessary.

Purpose—In March 2008, NIH program staff recommended that the VOICE protocol team discuss the stopping rules with stakeholders prior to initiating the protocol. The goals of the workshop were to inform community representatives about the potential ethical dilemma associated with stopping rules and engage in dialogue about these issues. We describe the resulting community consultation and summarize the outcomes.

Methods—A 2-day workshop was convened with the goal of having a clear and transparent consultation with the stakeholders around the question, 'Given emerging evidence that a product could prevent some infections, would the community support a decision to continue accruing to the trial?' Participants included research staff and community stakeholders. Lectures with visual aids, discussions, and exercises using interactive learning tasks were used, with a focus on statistics and interpreting data from trials, particularly interim data.

Results—Results of oral and written evaluations by participants were reviewed. The feedback was mostly positive, with some residual confusion regarding statistical concepts. However, discussions with attendees later revealed that not all felt prepared to engage fully in the workshop.

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Limitations—This was the presenters' first experience facilitating a formal discussion with an audience that had no advanced science, research, or mathematics training. Community representatives' concern regarding speaking for their communities without consulting them also created a challenge for the workshop.

Conclusions—Open discussion around trial stopping rules requires that all discussants have an understanding of trial design concepts and feel a sense of empowerment to ask and answer questions. The VOICE CWG workshop was a first step toward the goal of open discussion regarding trial stopping rules and interim results for the study; however, ongoing education and dialogue must occur to ensure that all stakeholders fully participate in the process.

The Issue

The goal of clinical research is to provide clear evidence of meaningful benefit for an intervention tested in a trial. In infectious disease prevention research, the aim is to reduce acquisition of disease using interventions that can be implemented in the at-risk population. From a public health point of view, interventions must prevent disease transmission/acquisition among the entire population at risk and must be cost effective, accessible and sustainable. However, challenges arise when a prevention method is only modestly/partially effective and when, at the same time, behavioral factors can affect the risk of disease. Access to a preventive intervention can affect behaviors in diverse ways, including the possibility that risk behavior may increase among some individuals after the public becomes aware that a new intervention is available. If the increase in risk is a real possibility, an intervention introduced into a population should have sufficient effectiveness to outweigh possible increases in risk behavior—otherwise the new intervention may not have a positive impact on incidence at the population level. And, as with any new technology, the public health benefit must outweigh the cost and burden on health care infrastructure and potential risk of side effects. Therefore, there is a need for caution in declaring "proven effectiveness" of a partially effective prevention technology due to three factors: the potential for increased risk behavior, the safety risk to healthy participants, and the cost and burden on the public health system. The aim of clinical trials in this setting must be to demonstrate a level of benefit that is sufficient to outweigh these concerns.

This was the situation faced by the Microbicide Trials Network (MTN) team developing VOICE (Vaginal and Oral Interventions to Control the Epidemic, http://www.mtnstopshiv.org/node/70). VOICE is a Phase 2B, five-arm, double-blinded, placebo-controlled, multi-site, randomized trial designed to compare the safety and effectiveness of oral and topical pre-exposure prophylaxis (PrEP) for prevention of sexual transmission of HIV. The study will enroll approximately 5000 women at various study sites in Africa and will test tenofovir microbicide gel and oral tenofovir and oral tenofovir/emtricitabine. Although the oral drugs are widely used with excellent safety profiles in the setting of treatment of HIV infection, they have some risk of kidney, liver and bone toxicity. In the treatment context, the benefits of the oral drugs outweigh concerns about toxicity, but if these drugs are used by healthy people for prevention of HIV infection, even moderate toxicity may be unacceptable.

At a policy level, making new HIV prevention modalities available on a population level will require financial and infrastructure investments. When biomedical products such as microbicide gels or oral PrEP are used for prevention, adequate safety monitoring and management are needed, in addition to a consistent and affordable drug supply. Having accurate estimates of effectiveness from clinical trials is critical for informing decisions by funders and ministries of health on whether to support the broader distribution of a drug in a prevention role. For example, if a clinical trial provides data showing that a microbicide gel or oral PrEP agent is 50% effective, but the confidence intervals surrounding that estimate

are broad (5%–80%), we cannot be confident that the true public health benefit of that intervention will offset the costs and risks of widespread implementation. If the true effectiveness of a product is near the lower bound of the effectiveness estimate (10%), it is unlikely to provide enough public health benefit to justify the costs. This reasoning suggests that clinical trials of new prevention modalities should provide conclusive evidence of substantial effectiveness against HIV.

A separate relevant concern is the strength of evidence used for regulatory decision making. Traditionally, regulators have required at least two well-controlled trials demonstrating statistically significant benefit in order to approve products for marketing. In a research field like HIV prevention, conducting a second placebo-controlled trial of a product which has a real chance of preventing HIV infection in an at-risk population may be ethically problematic. Some trials are designed to provide enough statistical power to enable regulators to make decisions based on one trial rather than the traditional two trials. In this article we describe consultations on the degree of benefit needed at a population level in a public health program, and do not explicitly consider regulatory decision making or the one-versus-two-trial standard.

Most trials of interventions are designed to prove whether or not an intervention is any better than a comparator—either a placebo or a competing intervention—addressing the traditional null hypothesis of no benefit at all. For VOICE a higher bar is being set: proving the intervention will, at a minimum, prevent a substantial fraction of infections to offset the potential risks and burdens noted above. To that end, the VOICE team has chosen to define “substantial effectiveness” as a reduction in risk of infection by at least 25% (preventing at least 1 in 4 infections). This would be analogous to the concept of “clinically significant effectiveness” in the context of treatment (rather than prevention) interventions. When the lower bound of the confidence interval on effectiveness is between 0% and 25%, this is considered evidence of “partial effectiveness,” and not “substantial effectiveness,” reflecting the belief that the effectiveness near the lower bound would not be substantial enough to justify implementation. Effectiveness trials of HIV vaccines also tend to be designed with a non-zero null hypothesis and generally have adopted a similar standard (30% efficacy).

Conducting an HIV prevention trial using a positive-offset null hypothesis (i.e. a null hypothesis greater than 0% effectiveness) could lead to a dilemma in the interim monitoring of efficacy. The trial may reach a point when an arm has achieved proven benefit, but the emerging evidence is not strong enough to support a minimum 25% benefit. In other words, the intervention is proven effective in reducing infections relative to placebo, but it is not yet clear that the product prevents at least 1 in 4 infections.

At this interim point in the trial the Data and Safety Monitoring Board (DSMB) would then face the dilemma of knowing the product has some positive effect, but perhaps not as great an effect as the protocol has declared necessary. The board might decide it is appropriate to announce the finding. Doing so, however, would in all likelihood make it impossible to continue the trial as designed, leaving unresolved the primary question of whether the reduction in risk is at least 25%. The alternative for the board is to recommend continuing the trial, taking the position that rejection of the traditional null hypothesis, but not the positive-offset null, is not sufficient evidence of meaningful benefit for this intervention.

Implications of the trial design for participants and their communities

Information given to volunteers in trials explains key technical concepts and various procedures that volunteers will need to undergo but avoids technical detail. Usually the following is explained to volunteers: “We do not know if the intervention in this study will provide benefit, or not. If new information becomes available that might be relevant to you

in deciding whether to continue your participation in this study, the researchers will tell you about it" [1, 2].

This presentation seems adequate for the case of the traditional no-effect null hypothesis. There is no attempt to explain to the volunteer the importance of continuing a trial despite emergence of a promising trend, nor is there an explanation that the trial will only be stopped once the trend achieves statistical significance relative to the criterion or criteria specified in the protocol. The researchers delegate responsibility for watching trends to an independent DSMB and do not themselves become aware of the "new information" referenced above until advised by the DSMB (and study sponsor) that the result is conclusive. (Note that the same reasoning applies in the case of a trend for harm, although of course the DSMB would not necessarily wait for evidence of harm to be highly statistically significant before taking action.)

Without formal interim efficacy monitoring, no particular dilemma arises due to the use of a positive-offset null hypothesis. The researchers are still obliged to share consequential new information with volunteers and community but, by design, they will not know interim trends from their own study. At the end of the study when the data are analyzed, researchers can evaluate whether the study demonstrated "partial" effectiveness" (some benefit but not at the level required by the trial) or "substantial effectiveness."

The situation is very different for the positive-offset null hypothesis in the context of interim monitoring. The informed consent information provided to the participants above makes no distinction between partial and substantial effectiveness. It is not obvious that volunteers would agree with the researchers that a trial should be continued once partial effectiveness is demonstrated at interim monitoring. Once the interim data allow rejection of the traditional null hypothesis, intuitively it would seem that the burden is on those who do not want to disclose that information to explain why volunteers are not entitled to have it. The assumption that disclosing to volunteers and community would effectively make trial completion impossible may not justify withholding such information. This realization led to National Institutes of Health (NIH) staff and the DSMB for the VOICE trial recommending dialogue and consultation with study communities prior to protocol/trial implementation to address the fact that interim findings that emerge may not (by design) lead to stopping of the trial.

It might well be the case that for the VOICE trial, and many other trials, participants in the control arm could not have immediate access to the active intervention following a conclusion of clinical benefit, and therefore cannot make immediate use of the new information, regardless of whether a traditional zero or positive-offset null hypothesis was being tested. There may simply not be any supply of the intervention product immediately available for trial participants; reasons for this could include need for regulatory approvals, manufacturing scale up, infrastructure, or high product cost. Nevertheless, community members could feel they had been misled by the traditional presentation of uncertainty about product effectiveness at the outset of the trial, when the trial is continued past the interim monitoring time points when new information was, in fact, available to the DSMB.

While clinical trialists and sponsors felt it was reasonable to set a high bar for effectiveness of the products tested in VOICE, it was equally important to discuss the rationale for that standard with community representatives. Trialists, sponsors and statisticians were then faced with the challenge of communicating the standard for effectiveness to community representatives engaged in plans for implementation of VOICE. Serious dialogue on the concept of sufficient effectiveness would need to take place before starting the trial, not

during the trial when even raising the issue would likely disrupt and perhaps damage the trial itself.

In March 2008, an internal group of NIH program staff recommended that the protocol team discuss the potential dilemma that may be faced at interim monitoring for VOICE and the trial's stopping rules with stakeholders prior to initiating the protocol. They noted that "discussion of the rationale up front might help to alleviate concerns that may arise during the course of the study about whether or not the participants in the trial are adequately informed about interim findings (if any) and about whether risks to these participants have been minimized." Critical to the process would be the inclusion of Community Advisory Board (CAB) members from each of the participating Clinical Research Sites (CRS).

In a tradition started in the early days of US AIDS activism in the 1990's, all clinical trial units funded by the Division of AIDS (DAIDS) are required to establish and support a CAB for each CRS. The CABs work in partnership with investigators and staff to provide a local perspective and feedback from the community regarding the research. In the MTN, each CRS ensures dedicated community educator (CE) staff time; the primary responsibility of the CE is to coordinate the community participation program for the site. More recent guidance provided in "Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials" (2007), a document that was drafted by a multidisciplinary international group convened by the Joint United Nations Program on HIV/AIDS (UNAIDS) and AIDS Vaccine Advocacy Coalition (AVAC), reinforces the importance of these activities. The document states that that "outreach and education efforts are key to build capacity and contribute to the empowerment of these communities as decision-making agents and advocates in the research process" [3].

Within these mandates, CEs and CABs in the MTN are called upon to work closely with study staff and the community from pre-implementation through study close-out. During the pre-implementation phase, community representatives identify and address rumors, misconceptions, or other issues that may hinder a smooth activation. A key component of the pre-implementation phase is community education, outreach, and dialogue regarding clinical trial concepts and the protocol. Once there has been community understanding, acceptance, and approval, CEs work with community members within the recruitment areas to facilitate recruiters' access to potential participants. On an ongoing basis, CEs work with study staff, CABs and participants on accrual, retention and adherence efforts and strategies. Finally, prior to close of the trial, the CEs and CABs are instrumental in ensuring that community and participants are updated on results dissemination plans and that study results are appropriately communicated to stakeholders. Because of the CAB role as the liaison between the community and the CRS, it was clear that the first step towards educating the community and volunteers would be the education of the CEs and CAB members.

To that end, a 2-day workshop was convened at a conference center near Johannesburg, South Africa on July 30 and 31, 2008, to discuss 1) the potential dilemma at interim monitoring, and 2) the stopping rules for VOICE and how they had been constructed. The primary goal of the workshop was, at a minimum, to inform community representatives about the potential ethical dilemma associated with stopping rules and engage in dialogue about these issues. The hope was to come to a consensus regarding the potential for the trial to be continued even in the face of proven effectiveness at an interim monitoring review.

Description of the Workshop

Invitations to the workshop were extended to MTN Community Working Group (CWG) representatives (CEs, CAB members) and other network members working on the VOICE trial. The thirty MTN participants included CAB members, CEs, advocacy group

representatives, research team members, and NIH (sponsor) staff. Although all of the meeting participants had been involved with microbicide research to some degree and many had worked on Phase 2/2B microbicide trials, their roles and experiences ranged widely from local community representatives with no advanced science, research or mathematics training to network investigators and statisticians who were well versed in the field of clinical research and statistical methodology. None of the community representatives had any prior education regarding stopping rules in HIV prevention trials that were measuring effectiveness.

Consultation with the community stakeholders meant being able to reframe for the MTN CWG the dilemma that the DSMB might face during an interim review: given emerging evidence that a product could prevent some infections, would the community support a decision to continue randomizing women on the trial and to withhold the early result from those already participating to gain evidence of better prevention effect? It was believed that genuine engagement required an education in the reasoning behind the monitoring guidelines of a trial, which meant discussion of the foundations of clinical trials research and design, including:

- generalization of conclusions from a clinical trial
- the role of the DSMB
- the special concerns surrounding the use of antiretroviral drugs typically used for treatment of HIV in the context of HIV prevention
- the guidelines used in interim monitoring (requiring an appreciation of the foundations of statistics, such as sampling variability and the interpretation of confidence intervals).

These topics were the basis of the workshop objectives, which were to engage in discussion regarding:

- the process for designing and conducting research to answer questions such as
  - “Is this safe?”
  - “Will this work to prevent HIV transmission?”
  - “Will people use it?”
  - “How will people behave if PrEP is believed to prevent infection?”
- how “risk” is defined and how we will measure effectiveness in “at-risk” groups in order to be confident that we have answered the question, “does it work?”
- the various levels of effectiveness that might be acceptable to different stakeholder groups
- the role and function of a DSMB: why it is needed and what its responsibilities are.

The 2-day workshop was divided into 13 sessions that lasted from 45 min to 2 h. Sessions were conducted using participatory methods and included lectures with visual aids, group discussions and exercises using interactive learning tasks. There was a progression in the complexity of the content of the presentations. Topics and concepts more likely to be familiar to the CWG, such as “How do we ask research questions in studies?” appeared early in the agenda. Discussion of concepts that were less familiar to the CWG, such as “Trials, Samples and Variation,” followed.

Two sampling exercises (using beads, a bowl and a perforated paddle) were introduced for concrete demonstration of sampling variability and confidence intervals. Although the

"truth" in the bowl (the proportion of colored beads) remained the same for every sample, the answer from each sample had intrinsic variability. The lesson for this exercise was the idea that a trial result is only a particular example of the variable results that could be observed.

The second sampling exercise was conducted to explain the meaning of a confidence interval, specifically that the confidence interval contains the range of plausible "true" values of the population characteristic of interest, in light of the data observed. This exercise was a critical part of assisting the CEs and CAB members to understand the rationale for the stopping rules in VOICE. Organizers hoped to facilitate the meeting attendees' understanding of the fact that as long as the confidence interval included a low value such as 5%, it is plausible that the intervention (a microbicide gel or oral PrEP) is only preventing 5% of HIV infections.

This effort to enhance the knowledge base of VOICE CEs and CAB members acknowledged the key role that they play in messaging the meaning of potential trial results. However, this was a novel expansion of their role in understanding, communicating and providing feedback on the statistical considerations and stopping rules outlined in the protocol which would define the final trial results. The 2-day workshop in Johannesburg was an optimistic first step in expanding the knowledge base of the CEs and CAB. The meeting outcomes and lessons learned from this initiative will be important in realizing the broadened role of CEs and CABs.

Meeting outcomes

Given the novelty of this event both for researchers and CWG members, there was no obvious metric for evaluating success. While it was clear that one objective was to facilitate CWG members' understanding of clinical trial design concepts, beyond that, evaluating the success or failure of the discussion of stopping rules issues in VOICE was relatively subjective. Written and oral evaluations were reviewed. Feedback from CWG members on the meeting and its content was mostly positive, and consistent with appreciation for the efforts of the instructors. However, attendee comments did note some residual confusion with the statistical concepts covered, in particular the idea that confidence intervals could represent a range of uncertainty around a "truth."

Examples of some of the written comments from the participants include:

> "It was an important workshop hence more time needed to explain about truths."
>
> "The facilitators had patience with the participants to make us understand the difficult topics."

While researchers and CABs have traditionally worked together closely on the challenges of implementing research protocols at the community level, CABs are rarely consulted about technical study design issues, and probably almost never about statistics. Therefore, this consultation reached into new territory for all groups (CWG members, investigators, research staff, statisticians, and NIH staff). The protocol team members and DSMB representative had designed presentations which attempted to break down statistical concepts into language and analogies accessible to community members without a scientific background, but there was no clear roadmap about how material could be presented in a compressed format to individuals without previous experience of these technical issues.

At the opening of the meeting a sense of optimism and inquisitiveness among CWG members could be felt regarding the forthcoming learning experience. As the 2-day meeting continued, researchers and community members shared a sense of uncertainty about whether

the communication efforts would be successful and about whether meeting objectives, namely, having a clear and transparent discussion about the stopping rule issues in the VOICE trial, would be feasible. As the meeting progressed, the community members' comfort and confidence were gradually replaced by suspicious curiosity, as unfamiliar research concepts such as efficacy, confidence intervals and point estimates were introduced.

> "The information was well received though complex. Please send us hard copies to explain complex information like confidence intervals."

Recognizing their responsibility to share learning experiences with peers at their respective clinical research sites and communities, community members felt pressured and unsure of themselves when requested by the researchers to convey the level of effectiveness of active study products that would be acceptable to them. Responding to this request in the absence of obtaining input from colleagues at home–as this is what community involvement means–would have been inappropriate.

> "During the first two days I have learnt a lot of things and I will take the knowledge to my fellow CAB members back home."

The session participants such as the CAB members and community educators who had the least knowledge about stopping rules were concerned that they were being given responsibility for educating the community and other stakeholders. At one point during the meeting, the community staff and community members were able to meet without the researchers to discuss the purpose of the meeting and the expectations the leadership had for the community staff and CAB. It was agreed after a lengthy discussion that it would not be appropriate for them to speak for their communities without first consulting them.

> "Challenging when asked to make a decision but useful to have discussed the issues of effectiveness as a CWG only."

Community members later expressed that it was very difficult to ask questions in the meeting, where senior research experts were presenting new, highly complex material and where the community members wanted to make a positive impression. There was also a sense of frustration among some in the community that the meeting had been organized and convened at a late stage in the protocol design process; they felt that if statistical and scientific concepts had been taught and discussed over many months throughout the protocol development stage, discussions about stopping rules at the finalization of the protocol would have been more accessible to the community.

Interestingly, the researchers did not become aware of community frustrations at the meeting until long after the fact, highlighting the difficulties in creating frank communication amongst the two groups in a setting where each group placed a high priority on courtesy and diplomacy. During and immediately following the meeting, many of the meeting's speakers were surprised at the readiness of CWG members to appreciate the importance of determining whether a prevention approach will confer a *substantial* risk reduction, rather than being interested in the licensure of a product that decreased risk of transmission at any level. However, in subsequent informal communication from workshop participants it became apparent that levels of comprehension for these concepts (e.g., different levels of risk reduction) were likely quite variable at the time among the CWG members.

Lessons Learned

The initiative to deepen the relationship between clinical researchers and community representatives through the education of the CEs and CAB can enhance the design and conduct of clinical trials, especially if part of a comprehensive program with multiple

learning opportunities tailored for community representatives. The presenters approached the goal of a transparent discussion and consensus building regarding the potential ethical dilemma for VOICE by first providing education in statistics and trial design. In the context of a formal scientific presentation, it can be daunting for anyone, but particularly for a CE or a CAB member, to draw attention by asking a difficult question or clarification on a point being made. The lesson here is threefold: 1) researchers need to create ongoing and regular educational opportunities for CEs and CAB members so that complex material can be taught sequentially over a reasonable time period; 2) scientists need to tailor their presentations to make them more accessible to CEs and CAB members; and 3) the presenters need to evaluate participant engagement and comprehension of the material presented, and adjust the style or content in real time to facilitate increased awareness and understanding by the audience.

The format for the presentations is very important, and the format of this training provided a good start with the mix of lecture, large-group discussions and hands-on exercises. Future sessions may benefit from incorporating a greater number of small-group discussions, asking CEs to assist in the development of the training, and continuing to find concrete ways – such as the sampling exercise -- to explain and demonstrate the more abstract ideas. Particularly helpful would be to relate the topic to other ongoing clinical trials that are already familiar to the group. Because the research and statistical concepts are unfamiliar to the community, there is clearly a need to repeat the training to reinforce the concepts and enrich the conversation in different settings with CEs and CAB members.

CEs benefited from a new awareness and understanding of the role played by the DSMB in monitoring a trial; many CEs had experienced early termination of a trial in their community [4]. With a basic understanding of the importance of monitoring, and the rigor and intent of DSMB deliberation, CEs and CAB members will be better prepared to prevent misunderstanding and mistrust with the community during ongoing trials or in the event of early trial termination. In addition, the opportunity for network leaders to better understand the perspectives and concerns of community members regarding possible study outcomes prior to the initiation of the study was of great value. During the consultative process, the CWG members taught network leaders that members of the community at risk clearly understood the need for adequate data on risks and benefits of a new prevention method so that this information could be accurately provided to future users.

Although VOICE had already been fully developed as a protocol by the time of this meeting, the success of this initiative reinforces how critical it is for there to be a more informed consultative process from concept/protocol development through activation. CWG members provide input early in protocol development process for MTN but, lacking a complete understanding of the science behind the protocol, that input is often limited. It is incumbent on all team members throughout the protocol development process to consider opportunities for education on the more technical aspects of clinical trials, to speak up when issues are not clear, and to maintain an open and productive dialogue. Network leaders and funders need to incorporate planning and support for ongoing opportunities for this kind of research education for community educators, CAB members and advocacy group representatives.

Having noted the level of interest by CWG members in the topics presented, the MTN leadership decided to devote time and resources towards continuing capacity-building activities for the MTN CWG. A review of relevant concepts took place at the 2008 MTN Regional Meeting in Cape Town, South Africa, and a follow-up review occurred during the VOICE Central Investigators' Meeting in Johannesburg, South Africa in March 2009. At the March 2009 meeting, a number of the CEs who had participated in the July 2008 workshop

noted a new level of understanding of the information. Many CWG members expressed an interest in more regular and ongoing educational sessions on statistical and scientific concepts in clinical trial design, and commented on a new appreciation for design issues in clinical trials of which they had previously been unaware.

Discussion during the workshop focused primarily on understanding how statistics is used to assess the level of benefit observed in the trial. Community members expressed clear preferences for having a high standard for success—a gel or tablet must be highly effective in order to be implemented in the community. What was less clear was how to evaluate what obligations we might have to women participating in the trial as the evidence accumulates. Given the challenges of grappling with statistical stopping rules, understanding of the notion of partial effectiveness might be enhanced by considering the concept of community equipoise [5]. Equipoise has often been considered the domain of health care providers: a community of physicians might have views about whether or not a treatment is proven effective, based on research and medical practice. Patient and advocacy communities have also weighed in on equipoise, expressing views about whether an intervention is deemed effective enough for implementation, sometimes disagreeing with clinicians. Advocates have expressed views on what kinds of trials are needed to provide convincing evidence.

Engaging in discussions around trial stopping rules and community equipoise poses major challenges, since community advocates and representatives need to be well equipped with an understanding of clinical trial design concepts, and researchers and clinicians need to understand community perspectives and values. However, the benefit of these discussions should not be underestimated. Community and researcher dialogue on questions of equipoise and trial design provides the best opportunity to advance public health while satisfying both scientific and ethical demands.

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Acronyms

CAB	Community Advisory Board
CE	Community Educator
CWG	Community Working Group
DAIDS	Division of AIDS
DSMB	Data and Safety Monitoring Board
HIV	Human Immunodeficiency Virus
MTN	Microbicide Trials Network
NIH	National Institutes of Health
PrEP	pre-exposure prophylaxis
VOICE	Vaginal and Oral Interventions to Control the Epidemic

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