vary, multiple trials can be of benefit by either repeatedly reinforcing or repeatedly disputing the general validity of particular results. Some trials test rather similar preparations, and several wisely use the same placebos.

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Risks in the Use of an Unblinded-Control Group
To the Editor—The article by Fleming and Richardson, entitled “Some Design Issues in Trials of Microbicides for the Prevention of HIV Infection” [1], highlights some of the challenges in conducting microbicide clinical trials. Fleming comments on these challenges from the perspective of one who is (1) lead statistician for the HIV Prevention Trials Network, which shortly thereafter initiated a Phase 2b study of 2 potential microbicides, and (2) a consultant to the US Food and Drug Administration. We focus specifically on Fleming and Richardson’s position with regard to including a third arm, an unblinded-control group, within a trial.

First, Fleming and Richardson assert that one of the major merits of the use of an unblinded-control group is that it will provide an estimate of “condom migration” (a term used in the microbicide field to describe a change in condom use—specifically, a decrease that is due to the availability of other HIV-prevention options, a decrease that may, in turn, affect the “real world” effectiveness of a given microbicide). However, true microbicide effectiveness and condom migration will not be addressed by the “condom-only” arm of a clinical trial, because (1) the study population will be very highly selected and, therefore, totally unrepresentative of all at-risk women in the study communities and (2) there is little volition involved in women’s decisions to use or not use the microbicide in the context of a trial, whereas study participants are instructed to use the product and are thoroughly counseled on safe sex. Furthermore, concern about condom migration seems inappropriate in sub-Saharan Africa, where condom use remains low despite high rates of disease [2] and educational programs about prevention [3].

Mathematical modeling has shown that condom migration would have an insignificant impact on the spread of HIV if the preexisting condom use were low [4]. Because a clinical trial is a controlled experiment, we should not expect that the outcome is directly representative of what will happen in the real world, should a microbicide become approved [5].

Second, adding an unblinded-control group increases a trial’s cost by more than half, because of the loss of power for multiple-comparison penalties [6]. Trials using unblinded controls are usually conducted when no reasonable placebo is available. Although a true placebo may be impossible to obtain, reasonable placebos for microbicide trials do exist. Furthermore, the possible effect of the placebos is likely to be very minor, in comparison with the effect that we would expect an efficacious microbicide to have.

Third, the use of an unblinded-control group threatens the study because all groups are not treated exactly the same [5], and this disparity may introduce condom use that is different from that in the gel-using group(s), the very phenomenon that the use of an unblinded-control group is designed to quantify. This disparity is problematic specifically because the lack of surrogate end points for HIV means that neither the use of condoms nor the use of microbicides can be reliably assessed. There exists the risk that an unblinded-control group will perceive themselves as benefiting less from being included within a clinical trial—because they receive no gel whereas the other 2 groups do receive gel—and this perception may both introduce gel sharing and increase loss to follow up in the unblinded-control, non-gel-using group, which, in turn, has the potential to introduce bias into the evaluation of the microbicide’s impact on the risk for HIV.

Finally, the efficacy of a product has a major impact on the motivation to use it. Although the urgent need for an available, effective microbicide is greatest where the products are currently being tested, the goal is to make them available globally. The use of a microbicide that has been proven to be efficacious will vary by location, because of differences in attitudes and behavior. However, the use of a microbicide that has unknown efficacy (e.g., when it is being tested in a clinical trial) will likely be different than the use of a microbicide whose efficacy is known (e.g., once efficacy has been quantified and the product is on the market). This difference will cause a difference in effectiveness. Real-world effectiveness, therefore, cannot be reliably assessed before efficacy is known but, rather, should be researched by using other trial designs in post-marketing studies.

In summary, many of Fleming and Richardson’s arguments for including an unblinded-control arm within a trial overlook obvious concerns about how the data generated by such an arm should be interpreted. As a result, the most compelling
reasons for including an unblinded-control arm are reduced to academic interests regarding individual behaviors in the context of clinical trials. Given the urgent need for the identification and mass promotion of an effective microbicide, there may be better uses of time and resources than including an unblinded-control arm within a trial. Current microbicide trials should address efficacy, in an effort to pave the way for future trials focusing on effectiveness. We thank Fleming and Richardson for raising some interesting points about this important topic.

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Reply to Skoler et al. and to Stein and Susser

To the Editor—In our article on the design of microbicide trials [1], we discuss 3 challenging issues. The first relates to the relative benefits of the use of both blinded and unblinded controls, including the need, in some settings, to consider the use of both. In response to 2 recent letters regarding our article [2, 3], we provide further clarification of the relative utility of these 2 types of controls.

The use of blinded controls provides a preferred approach in many clinical settings [1]. However, it is neither a “fundamental requirement” nor an “ironclad rule” that control groups be blinded. In fact, there are settings in which the use of blinded controls would not be ethical, such as when the interventions being compared are readily identifiable because of differences in risks of serious toxicities; for example, an experimental drug for the treatment of cancer may be known to induce high rates of significant adverse events, such as alopecia, stomatitis, myelosuppression, hepatic toxicity, or nausea and vomiting. In such settings, the use of unblinded controls has enabled unbiased evaluations of objective outcome measures, such as patient survival.

In some settings, such as when the placebo is not inert, the use of blinded controls may lead to biased results. In the setting of microbicides administered for the prevention of HIV infection, where there have been no trials with both blinded and unblinded controls, data do not exist that would reasonably reliably establish any placebo regimen to be inert. In fact, one might wonder whether the broadly unimpressive results that thus far have been reported for microbicide regimens evaluated in placebo-controlled trials are due, at least in part, to the fact that the placebo regimens could be carrying some important benefits of the microbicide regimen, including lubricating and/or physical-barrier effects, the presence of preservatives having microbicidal effects, the alteration of the vaginal microflora, or decreased concentrations of HIV-infected semen in the female genital tract. Unless an inert placebo is used, one is unable to obtain an unbiased estimate of efficacy.

There are additional settings in which the use of blinded controls may not lead to fully informative results, such as when one wishes to estimate the effectiveness of the intervention [1, 4]. But will estimates of effectiveness that are based on comparisons with unblinded controls be generalizable if (1) the study populations in clinical trials are “highly selected” or “totally unrepresentative” of the overall population at risk or (2) the adherence to study interventions does not match what could be expected in the real world? In trials conducted under such conditions, neither a placebo-controlled estimate of efficacy nor an estimate of effectiveness based on a comparison with an unblinded control would be broadly generalizable. Participants selected for clinical trials should be a reasonable match with the population targeted to use the intervention in the real-world setting. Adherence to the experimental intervention (such as the use of topical microbicide) and to ancillary care (such as the use of condoms) should be similar to the best that is practically achievable in a real-world setting. Establishing the real-world benefit-to-risk profile of an intervention, rather than simply establishing “proof of concept,” should be the goal of a registrational trial in a regulatory setting.

It has been suggested that one might evaluate efficacy in a registrational trial and defer the determination of effectiveness until after the intervention has been marketed. Yet, how would one conduct a post-marketing trial comparing a microbicide regimen having established efficacy against an unblinded “condom-only” control?

Achieving high levels of retention also is an important issue in obtaining reliable conclusions. Will it be difficult to follow participants who are randomized to an unblinded “condom-only” control arm? Fortunately, it has been possible to achieve...