Control Groups in Microbicide Trials: In Defense of Orthodoxy

To the Editor—The Journal recently published 2 commentaries on the design of trials testing the effects of microbicides against HIV and other venereal infections. Both commentaries propose that, in addition to a blinded-control group, a second control group—which would remain “unblinded” as well as untreated—should be included within such trials [1, 2]. The additional control group—named “condom-only” or “non–gel-using”—would undergo the same recruitment procedures, follow-up, and counseling that are used in the other arms but would not be subject to further intervention. We think that this approach is mistaken. The design retains one fundamental requirement of such trials—namely, random assignment—but abandons another—namely, “blinding” [3]. We foresee 2 problems and, to address them, bring forward 2 arguments.

The first problem relates to the standard against which protection is to be judged: a placebo, if not entirely inert, might give as much as or more protection than does the putative microbicide. Although comparisons between blinded groups are ordinarily sufficient to support conclusions about treatment effects, a result showing no difference could be ambiguous and allows 3 possibilities: both treatments could be equally effective, equally ineffective, or equally harmful—hence the justification for including an open “non–gel-using” arm.

The second problem stems from the considerable protection that proper condom use confers against sexually transmitted infection. Ethical research requires that investigators counsel at-risk women to insist on condom use in all sexual encounters. Should the women truly conform, reduced frequency of infection will render detection of microbicidal effects less likely. Reported condom use inevitably leaves actual use uncertain; moreover, among “gel-using” groups especially, differential misreporting may well conceal reduced condom use. To protect against such bias, both commentaries again recommend the use of an unblinded condom-only group as a “true” control, the better to represent the “real world.” We submit that an unblinded group can serve neither as a suitable substitute for a blinded control nor as a true representation of the real world.

With regard to the first issue—the use of comparison groups in controlled trials—all investigators well know that this standard aims to keep differences between the test group and the control group(s) apparent, both to the research teams and to the subjects; long-established and virtually ironclad rules insist on such double blinding, to avoid bias. By definition, an open arm violates this standard. Thus, open-arm subjects will surely be exempted from counseling and questioning routines on use of the prescribed gel. An open condom-only arm not only makes the disparity vis-à-vis the blinded-control and treated arms obvious to all investigators but can have untoward consequences. Thus, some field workers have found it more difficult to maintain subjects’ participation in a condom-only than in a blinded arm. Two concerns therefore remain unresolved: the intervention is not identical across groups and less-complete follow-up in open arms than in closed arms prejudices randomization and reduces statistical power.

With regard to the second issue—representativeness—normal research procedure almost invariably requires selected participants. In the situation discussed by the 2 commentaries, it is clear that the populations are selected in at least 4 respects: they have a limited age range, are seronegative for HIV, are active sexually (and prefer to avoid conception), and readily conform to a demanding procedure. Therefore, the sample does not necessarily fully represent the population that yields such subjects.

For the selected subjects, of course, awareness of their treatment status could influence their actual as well as their reported behavior, both of which are critically pertinent to the outcome of the trial. This is precisely a situation in which it is crucial to sustain blindedness among all participants. Blinded trials of microbicides are specific and particular in intent—they are a beginning and not an end. They test afresh, on the human scene, what has already been tested in the laboratory. They aim to detect the differences in effect between preparations, not to resolve speculation about what might happen later in one or another community in the real world. Some describe this stage of microbicide testing as “proof of concept” (a stage that necessarily precedes licensing considerations, which must furnish their own criteria [4]).

The choice of suitable controls is not solely an academic matter. Coplan et al. [4] are obviously correct to be concerned about the burdens that the use of an unblinded-control arm adds: it increases the number of subjects who must be recruited; it increases costs; it requires more-extensive analysis; and it requires both that the duration of the trial be prolonged and that the implementation of treatment be deferred. Multiple trials are under way, and they enhance the importance of economy in all senses. Although Gross has published a strong criticism of such multiplicity [5], advantages may derive from it; because test populations and their circumstances
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 placebo 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 been proven to be efficacious will vary by location, because of differences in attitudes and behavior. 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