9. Testing Second-Generation Microbicides

Framing the terms for the next generation

As of early 2005, five microbicidal products were in or entering late-stage clinical trials (see Chapter 2, Table 2 and Table 3). Meanwhile, another two dozen products are in earlier stages of testing. As first generation products move through effectiveness trials and beyond, new questions arise. How effective must a product be to warrant regulatory approval and introduction? How to assess the long-term safety and effectiveness of products already licensed? Will access to an effective product be guaranteed to participants after a trial? What are the implications of identifying a weakly protective product for evaluating second- and third-generation microbicides?

For new products to be licensed, drug regulators—especially the US Food and Drug Administration (FDA)—usually require at least two randomized controlled trials or one "pivotal trial" that provides as much compelling evidence of effectiveness as two trials. If a single trial shows evidence of effectiveness but does not yet meet standards for FDA approval, some countries may nonetheless license the product. Others may require a second trial, as would the United States.

Under such circumstances, some countries may call for "bridging studies" to look at the safety and acceptability of a new product for specific populations. Bridging studies usually require hundreds of participants, about the same as a Phase 2 trial; and they typically involve 6 to18 months of follow-up. It is not clear whether a control arm should be used in a bridging study or whether everyone should receive the product. Another challenging question is what should be said about the effectiveness of the product during the informed consent process. Although the initial trial may have generated some information about effectiveness, it is unlikely to have yielded sufficient evidence to provide clear counseling messages on how effective the product would be if used consistently.

Repeating the trial to confirm effectiveness raises similar questions. Given evidence of weak effectiveness, is it ethical to conduct a second trial that compares the test product and condoms to an inactive gel (placebo) and condoms? Specifically, some have argued that once evidence of effectiveness is shown, it is not ethical to repeat the trial in another setting or to plan and implement a similarly designed study of a new candidate microbicide.

Consultation participants spent considerable time grappling with the implications of this question for the design of second-generation microbicide trials. For example, suppose that a current trial in the field yields evidence of effectiveness. Would the new product then have to be given to all participants in future trials as defined by the basic standard of care? If so, what are the

implications for trial size and for procedures? Similarly, suppose that a microbicide is found to be effective in a particular population. Can and should the trial be repeated elsewhere if there is reason to believe that conditions influencing its effectiveness may differ in other populations? The group concurred that complex problems such as these will require reflection and debate stretching well beyond the Consultation.

Applying the standard of care argument

There are at least two ways to consider the "next-generation" questions. First, the problem may be framed in terms of standard of care. When does a new prevention tool become part of the "standard prevention package" that must ethically be provided to all participants in HIV prevention trials? Is it reasonable to consider something to be "standard care" before it is widely available outside clinical trials? If condoms and STD treatment provide excellent HIV prevention when used consistently, is it ethically necessary to add new methods to the background package of prevention if this makes the task of evaluating novel (but potentially better) interventions impossibly complicated and costly?

As discussed earlier, some ethics guidance documents recommend that research participants in the control arm of a trial receive the "best current prophylactic, diagnostic, and therapeutic methods" (Helsinki Declaration). By contrast, others demand "an established effective intervention" (CIOMS and NBAC Report), or "a universal standard of care… or at a minimum the best intervention available for that disease as part of the public health system" (Nuffield Council).

The ethical principle of equipoise

The second approach to framing the next-generation question is in terms of the ethical principle of equipoise. The term *equipoise* describes a situation where genuine doubt exists on whether one product or intervention works better than another. To understand equipoise, imagine that someone needs to decide whether it is ethically permissible to enroll an individual in a clinical trial. Assume that the decision-maker consults with experts in the field about available methods, concluding that there is considerable uncertainty about which is better. Perhaps this uncertainty is because the vast majority of experts agree that there is reasonable doubt about which method is better; or perhaps they strongly disagree among themselves on which is best, which also translates to a high degree of uncertainty. With no reason to unequivocally choose one option over another, and no other available intervention that would be more attractive, then enrolling individuals into either the experimental or the control arms would be considered ethical, and the trial may proceed.

While equipoise appears to be a straightforward concept, it is not easy to put into practice. In its application, there is much room for interpretation. Who decides, for example, when enough is known to weigh the options? Is equipoise related to the population and can it differ in different settings? Furthermore, equipoise is a necessary but insufficient condition for ethical research. If equipoise were obtained under unjust or exploitative conditions, the research could still be considered unethical—for example, despite genuine uncertainty on whether one or another poison kills human beings more quickly, it would still be unethical to implement an experiment to resolve the issue.

Alex John London, an ethicist from Carnegie Mellon University, used the concept of equipoise to explore scenarios that the microbicide field might face once trial data become available.[1] Take, for example, questions such as these:

1. *If a microbicide were found to be effective in one trial, would it be ethical to repeat the trial in another population*?

   According to London, the answer depends on how convincing the results of the first trial are and the differences between the two study populations. Some questions that would need to be asked:

   - Are the results of the first trial so robust as to leave no doubt about the effectiveness of the intervention?
   - Might methodological concerns over the first trial leave at least some experts unconvinced as to the findings?
   - Are the differences between the two populations or two trials sufficiently significant so that equipoise may exist for one but not the other? In other words, is there still uncertainty whether the microbicide would be effective in a different population—for example, one with more frequent sex, lower rates of STDs, and so forth?

   The "best" product or intervention for some is not necessarily the best for everyone. What's best for someone will hinge on that person's individual characteristics, environment, problems, and preferences in regard to the existing options—for example, ease of use or sensitivity to side effects. Significant differences in populations may create equipoise in the new trial situation—that is, uncertainty about whether the experimental product shown to be effective in one trial would really be better than the control arm for the new study population. In this situation, it would not be unethical to repeat the trial, with a placebo and standard prevention package in the control arm.

2. *In the case of a microbicide being shown to be effective in one trial, would it be possible to conduct a trial of a second microbicidal product in which the control arm is given condoms and a placebo, not the first microbicide*?

   Equipoise requires that no other method exists that would be a preferable option over any of those in the trial, including the placebo used in the control arm. The key questions would be:

   - After consulting with experts in the field, would a decision-maker have considerable doubt about which package would be better for the control arm—that is, the standard package (condoms and counseling) plus the microbicide that had shown effectiveness in an earlier trial, or the same package with a placebo instead of that microbicide?
   - Would withholding the first microbicide allow some infections that would not have occurred if the product had been given to trial participants?
   - Could providing the first microbicide together with condoms result in less

[1] Johnson, AL. Equipoise and second generation trials. Presented at: The International Consultation on Ethical Issues in the Clinical Testing of Microbicides. October 23–24, 2003; Warrenton, Virginia.

overall protection than if condoms and STD treatment only were provided in the comparison arm (for example, because fewer people try to use condoms)?

Implications for future Phase 3 trials: superiority and equivalence trials

Should it prove to be the case that ethics demands that any future microbicides be tested against existing microbicides (plus condoms), doing trials of second-generation microbicides might become extremely difficult and costly. The requirements for future trials will depend on a number of factors, including the degree of effectiveness of the first microbicide, the incidence rate in the study population, and the question the trial is intended to answer.

Generally, once an effective drug or treatment becomes the standard care for a condition, trials of new products are designed to prove that they are either equivalent to or better than the existing treatment. These trials, known as equivalence or superiority trials, require many more participants than do trials comparing a new treatment to a placebo.

To illustrate, Anne Colletti of Family Health International outlined how superiority and equivalence trials of a next-generation microbicide would work.

Superiority trial. If the researchers sought to show that a new microbicide were better than an earlier product, they would first select the degree of superiority they hoped to be able to measure (that is, the percentage that the second product is expected to be more effective when compared with the first). Assuming that the first microbicide, used as a control, is 33 percent effective and the trial is designed to show that the new product would be 33 percent more effective—or 55 percent effective compared to a true placebo—the trial would have to enroll 7,000 to 10,000 participants to achieve 80 to 90 percent power to detect the effect.[2] If the control were a placebo and condoms, instead of the first microbicide and condoms, the number of participants would be only 1,000 to 2,000.

Equivalence trial. If the goal were to show that the new product is essentially no worse than the first in terms of effectiveness, the researchers would choose a "targeted margin of noninferiority."[3] For example, if the first microbicide offered in the control arm of the study is 33 percent effective and the targeted margin of noninferiority is 10 percent, the number of participants would have to be in the range of 88,000 to 150,000 to achieve 80 to 90 percent power.[4] If there is a question about how effective the first microbicide might be in the population of the new trial, drug regulatory authorities may require both an "active control" (the first microbicide) and an "inactive control" (a placebo arm). Adding a third arm to the trial would increase the number of participants even more.

[2] This estimate makes a number of other assumptions about the trial and the trial site—for example, a 5 percent HIV incidence rate. A trial with 80 to 90 percent power to detect a 33 percent more effective product means that the trial has an 80 to 90 percent chance of detecting the effect, if it is there.

[3] The reasons that it might be worth looking at additional products with roughly the same level of effectiveness are many. A new product might offer advantages, such as being protective against other STDs, contraceptive/noncontraceptive, longerlasting, or lower cost.

[4] This trial would rule out that the new product is less than 26 percent effective.

As is the case with most of the toughest issues regarding the clinical testing of microbicides, answers to questions about future trials are neither straightforward nor obvious.

- Who makes the decisions about the requirements of these later effectiveness trials—for example, the degree of superiority or the margin of noninferiority, the strength of evidence needed, the appropriate control?
- What messages should be given about effectiveness in the informed consent process?
- Who will pay for these subsequent trials, and what are the implications for overall resource allocation?
- How can the concern for safety and the regulatory process best be balanced with the need to expand access to potentially life-saving products?

As the first products enter Phase 3 trials (and many more are in the pipeline), the most daunting question may be how to prioritize which products should move into effectiveness testing. What to do after one or two products show some, even if limited, effectiveness? Meanwhile, the HIV epidemic is a "moving target." It continues to evolve, affected by population movements, vaccines, therapeutics, and other factors. A microbicidal product that is relatively effective, for example in 2010, may not be as effective five years later—for example, if viral resistance develops against an antiretroviral drug used in the microbicide.