10. After the Trial: Continued Access and Post-Approval Studies

Post-trial access

According to international guidelines such as the Declaration of Helsinki and the European Group on Ethics in Science and New Technologies,[1] those who participate in clinical trials should receive continuing access to experimental products that are shown to be effective. This obligation is based on an ethical argument that no one should be withdrawn from a method or medication shown to be beneficial to her or him—all the more in light of the participant's willingness to assume risk as a contribution to the research. Ideally, effective interventions would be provided through the national health system of the country hosting the research. But that seldom happens in practice, especially if the new product is costly.

Obstacles other than cost can impede the research participants' continuing access to experimental products—for example, the time lag between conclusion of the trial and product approval by regulatory authorities. In most cases, additional trials are required before a new drug is approved for licensing. And even where regulatory hurdles are not at issue—for example, products approved for another use that are already available—many questions remain:

- *Who* has the obligation to provide the product or treatment—the study investigators, the sponsor, or the host country?
- Who will pay for it?
- How firm and far reaching does the ethical commitment have to be (for example, cash in the bank to pay for the product)?

As acknowledged by the Nuffield Council on Bioethics, "If researchers or sponsors were categorically required to fund the future provision of interventions, either to participants in the study or to the wider community, many would be likely to cease supporting research. In particular, sponsors from the public sector are unlikely to be able to bear the costs involved without curtailing other research (p. 40)."[2]

This scenario is likely to be especially problematic in the case of HIV treatment trials. The burden imposed by continuing provision of ART is even greater in treatment trials than with prevention trials because trials testing the safety and effectiveness of different treatment regimens in developing countries involve many more HIV-positive individuals than those testing vaccines or

[1] European Group on Ethics in Science and New Technologies. Opinion number 17 on the ethical aspects of clinical research in developing countries, January 2003; Available at: http://europa.eu.int/comm/european_group_ethics/docs/avis17_en.pdf.

[2] Nuffield Council on Bioethics. The ethics of research related to health care in developing countries: A follow-up discussion paper. London: Nuffield Council on Bioethics; 2005.

microbicides. In some prevention trials, fewer than 100 individuals might be expected to become infected during the course of the trial—far fewer than would likely be enrolled in a treatment trial. As a result, the need to sustain long-term ART at former treatment trial sites could easily overwhelm the donors' research budgets.

At the conclusion of trials, investigators should also anticipate the emotional and psychological needs of the participants. In South Africa, staff and participants in the Population Council's Phase 2 microbicide trial reported that some women felt "dumped" or abandoned at the end of the trial. Even among those who had been screened out of the trial, many maintained continuing expectations of trial staff. Consultation participants agreed on the need to not create expectations for continuity that cannot be met. Participants must carefully be "weaned" off the program. In this context, it is particularly important to strengthen local services to which participants can be referred.

Phase 4 studies

Once clinical trials have offered convincing evidence of a product's effectiveness, the licensing process begins. Until a product has been approved and is licensed, it cannot legally be made available, at least according to US regulations. The only way to continue to offer the product to the study participants, or to others, is to initiate a Phase 4 study. At this point, the data collection requirements are reduced and only "adverse events" are reported. Since one of the objectives is to expand access, everyone is given the product and there is no control arm. Phase 4 studies create the opportunity to continue to monitor safety, adherence, and effectiveness; to refine dosing recommendations; and to experiment with different applicators and counseling messages.

Some questions about Phase 4 studies:

- How long should they last? Two years? Five years? Until the product is licensed and available locally?
- What should participants be told about safety and effectiveness in the informed consent process?
- Who will provide the resources, and what are the tradeoffs and opportunity costs for financing of other trials?
- If Phase 3 study populations were rolled over into Phase 4 trials to not interrupt access, those sites would not be available for Phase 3 trials of other products. Would this be acceptable given the limited trial site capacity?

Other options for expanded access while waiting for licensing might include an Investigational New Drug Application[3] in which a new treatment product, which has been shown to be effective but has not yet been approved, is made available to people with life-threatening conditions for which no other alternatives are available. A similar parallel track allows a method under investigation to be provided to people too sick to enter clinical trials. Both of these strategies are justified for extremely ill individuals with no other recourse, so they may not be adaptable for prevention technologies.

After approval, Phase 4 studies may be implemented to consider special safety considerations or to look at effectiveness in

[3] An Investigational New Drug Application is a request to the FDA to allow a drug or product that is still in the research process to be given to humans.

different populations. The International Conference on Harmonization of Technical Requirements[4] recommends that researchers explore how a drug or treatment would act among different ethnic or age groups. This would include, for example, looking at the way a product would be absorbed or metabolized given "intrinsic factors," such as genetic differences, body weight, and organ functions. It also entails consideration of "extrinsic factors" in the environment or culture of the study population, such as climate, exposure to pollution, diet, tobacco use, medical practices, socioeconomic factors, and educational status.

Where is the end of the road?

Approval and licensing is far from the end of the road. As one Consultation speaker remarked, "Once we get to regulatory approval and can sigh with relief, we'll only be halfway there!"

What comes next? The introduction of any new pharmaceutical product poses a challenging new array of problems: manufacture, marketing, distribution, acceptability, and cost to consumers.[5] Guidelines must be developed for using the product, training curricula developed, and informational materials in multiple languages for the most- and least-sophisticated of audiences. Local regulatory requirements must be met. The logistics of procurement, storage, distribution, and service delivery infrastructure must be handled.

For some new products—for example, contraceptives—issues such as these were typically first worked out in pilot districts of a few countries and then scaled up. Yet some questions regarding introduction and access to future microbicides can and should be addressed now. For example, we could conduct research to understand and anticipate the concerns of intermediaries—government functionaries, pharmacists, and health professionals, the key people who will eventually mediate between the product and users. Programmatic and logistical needs can be explored. Studies conducted now can help to identify user attitudes across cultural settings. The wealth of materials that have been developed for informed consent can be adapted and tested for use in counseling situations.

Many questions are simply not answerable, and they will not be until an actual product with known characteristics is in hand. Yet once another microbicide is available, it can and should be more than "just another product." As the development of microbicides has already shown, technology can serve to raise ethical issues ranging from do-no-harm to social justice; and beyond protecting and empowering individual women, they can raise local standard of health care. Whatever else may be uncertain, the need for advocacy around issues of gender power, resource distribution, and access will continue unabated.

[4] Interestingly, although the International Conference on Harmonizaiton developed guidelines for evaluating "ethnic factors," as well as geriatric and pediatric standards, they have not developed any specific guidelines for the inclusion of women in research.

[5] McGrory E, Gupta G. *Preparing for Microbicide Access and Use*. Report of the Access Working Group of the Rockefeller Microbicides Initiative. New York: Rockefeller Foundation; 2002. Available at: http://www.global-campaign.org/clientfiles/rep6_preparing.pdf.