

7. Defining “Benefits” and “Standard of Care”

Among the thorniest ethical issues in clinical research on microbicides is the question: Which benefits should be provided—to whom and for how long? The challenge is, first, to define what is meant by “benefits” and then to properly balance these benefits against the risks and burdens of research.

The problem, in part, is that ethical discourse on appropriate benefits often refers to different things. Benefits can refer to the package of interventions offered to those in the trial’s control arm or to the health services offered to all trial participants during the research (referred to as the trial’s “standard of care”). The discourse on benefits can be further extended to include advantages offered to the wider community hosting the trial. Some benefits are tangible and immediate, such as access to improved health care; others may not materialize until far into the future (access to antiretroviral therapy (ART) if one becomes infected during an HIV prevention trial).

In terms of *material* benefits, no one disagrees that participants in a clinical trial should be reimbursed for costs such as transportation, time, and childcare; that they be given food while at the clinic; and that it is appropriate for them to receive gifts, such as T-shirts and tote bags, to mark milestones in the trial. It is also widely accepted that sponsors and investigators are obligated to provide medical care

necessary to implement the research protocol in ways that are safe and scientifically valid.

Controversy begins to creep in when discussing medical or social service benefits beyond those required to conduct the trial, or providing benefits to trial participants that would not otherwise be locally available. Some argue that benefits beyond compensation for time and effort constitute “undue inducements” and are thus ethically problematic. Participants may be motivated to join the trial for access to an experimental treatment that they need, or in hope of continuing access if an experimental product is shown to be effective. Similarly, they may be motivated by a desire for better ongoing health care than is otherwise available locally, or simply by cash. Some prospective participants may want to participate—or may be pressured to participate—so that their communities receive collective benefits, such as improvements to the local health care infrastructure.

Others argue that inducements, even relatively strong ones, are not necessarily problematic. Motivations such as altruism, curiosity, and the desire for access to quality care are neither a priori “wrong” nor morally problematic. Problems arise only when inducements become coercive—that is, they edge toward “offers that cannot be refused.” They become ethically problematic when they are so appealing as to impair proper judgment and cause a participant to ignore

or discount obvious risks. If people are implicitly pushed to do something that they would not do otherwise, the voluntary nature of participation is compromised, and inducements can be said to be “undue.”

Clinical research protocols must be approved by regulatory authorities and ethics committees who examine risk-benefit ratios to determine whether it would be against the interests of “reasonable persons” to participate. While the weighing of risks and benefits is subjective, this approval process works to ensure that the balance between risks and benefits does not tilt too far in one direction or the other.

The general worry over inducements may thus be overstated. An issue of greater concern may be distributive justice. Is it appropriate to provide benefits to trial participants that are not available to others? Does the provision of exceptional health care services to trial participants—but not to other members of their families or communities—breed discontent or exacerbate local inequities? If ART is provided only to those who seroconvert during the trial—but not to all who are found to be HIV-positive at screening—is the principle of justice violated?

After grappling for two days with these questions, participants in the Consultation generally agreed upon three conclusions.

1. Researchers do have a special obligation to the participants in their trials, and possibly to their communities. This obligation derives from the notion of reciprocal justice.¹ Participants give more of themselves; and thus, they qualify for special treatment.



¹ Reciprocal justice is a concept from ethics that says that someone who has benefited from the investment and sacrifice of others owes them proportional recompense.

2. Researchers are not solely responsible for meeting health care related needs of trial participants. The researchers’ obligation is to ensure that those who are screened or enrolled in trials have access to adequate health care, though not necessarily to provide it themselves.
3. Researchers should always try to reduce, not exacerbate, inequities. Nonetheless, disparities realistically exist everywhere in the world. To try to improve life for some—even if not for everyone—is not morally wrong.

Standard of care within trials: the debates

Consultation participants agreed that investigators (and their sponsors) ask a great deal of trial participants and therefore take on a special responsibility to them. Researchers have access to resources; they should use the opportunity of research to reduce suffering. In this view, the researchers’ obligations to the larger society do not trump their responsibilities to individual participants. To sacrifice the interests of trial participants in the name of science or for long-term social benefit is not ethically justifiable, even more so because these “benefits” are uncertain and may not materialize.

Yet specific questions persist:

- What is the appropriate standard of care or prevention package within the trial?
- What are the researchers’ obligations to those who seroconvert during the trial?
- What obligations are assumed for women who are recruited but screened ineligible for the trial—and how can these



obligations be met? (The number of women who are HIV-positive at screening may be significantly greater than the number who seroconvert during the trial.)

- What are researchers' obligations to local communities? To the host country?

The concept *standard of care* is rooted in the physician's fundamental ethical obligation to provide patients with the best possible care. It marks the boundary between expected standards of practice and medical negligence.

Over the past decade, the concept of standard of care has migrated into the general discourse of research ethics. In the context of clinical trials, it generally refers to one of two things: the general package of health services offered to individuals who participate in trials, or more specifically, the treatment or care provided to members of the control arm of a trial. In recent debates over placebo-controlled trials, the term has most frequently been used to refer to the treatment or care that should be offered to members of the control arm.

The debate in the clinical research, however, is over *which* standard of "best care" should be provided in the context of a trial. Is it the "best proven" treatment or intervention available globally (sometimes referred to as the "universal standard"²)? Is it the best care that is available locally (or at least should be, according to national health standards)? Or is it something in between?

In addressing this problem, most individuals agree that accepting local health-care realities—if these realities are grossly

inadequate—does not constitute a sufficient standard for ethical research. Yet how far beyond the local standard can or should investigators be expected to go? Is it acceptable to design studies to a standard that represents the highest level of care that could be sustained locally? Or, does justice imply that every person enrolled in a clinical trial—regardless of the local circumstances at the trial site—receive the same best-proven treatment that would be received if the trial were to take place in an industrial country?

An argument against requiring participants in the control arm to receive the best-proven intervention available globally is the need to answer a scientific question relevant to the host community. If community members participating in the control arm of the study receive a standard of care that cannot be sustained locally, the trial may not yield valid comparative data to assess the effectiveness of the experimental intervention. Those who take this position argue that many revolutionary public health interventions, including oral rehydration for childhood diarrhea, would never have been proven effective if effectiveness trials had been forced to compare this "low-tech" intervention against hospital-based, intravenous rehydration, which was the standard of care for severe cases of diarrhea in the industrial world.

Others argue this question in purely pragmatic terms. Whether or not it would be desirable for them to do so, researchers conducting clinical trials simply do not have the capacity to fully redress global disparities in health care. For better or



² The Nuffield Research Council, which introduced the term into research ethics, defines "universal standard of care" as "the best current method of treatment available anywhere in the world for a particular disease or condition." Others prefer "highest standard of care" in referring to the same concept.

worse, that responsibility lies with policymakers, governments, and donors. The role of the researcher is to advance knowledge with potential long-term benefits for a great many people, not provide short-term benefits to a small population who happen to be in a trial.

Those who favor providing the best-known intervention as the ethical standard argue that to do otherwise constitutes a fundamentally unjust double-standard and that participants not receiving the best-known interventions could suffer from preventable harm. Also, it can be argued that international research initiatives *are* legitimate vehicles through which global inequalities in access to health care can be reduced. Conforming to a universal standard also avoids inconsistencies in the care provided among different sites in a multicountry study. To achieve the necessary numbers, trials frequently enroll participants in many countries and sites and then pool the data for analysis. If all decisions are negotiated locally based on local realities, different people in the same trial could receive different levels of care.

The ethical basis for extending benefits to communities, rather than to trial participants, is less obvious. There is a certain amount of controversy on this matter, especially between research sponsors and the communities that participate in research. Ethics is, however, not the only grounds from which to argue this point. Both communities and countries should carefully consider how best to

negotiate the benefits to be received through participation.

International guidance on standard of care

International guidance documents are inconsistent in their positions on standard of care and appropriate use of placebos. The most frequently cited document, the Declaration of Helsinki, contends that the best-known methods of treatment, diagnosis, and prevention should be provided. Paragraph 29 states:

The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.

Yet an exception may be made under certain circumstances. In November 2001, the World Medical Association (WMA) clarified Paragraph 29 as follows:

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method.³



³ "World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects," Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended most recently by the 52nd WMA General Assembly, Edinburgh, Scotland, 2000. This is an amendment in the form of a footnote to Paragraph 29, approved by the WMA General Assembly, Washington DC, 2002.



Paragraph 29 of the Declaration of Helsinki has been widely interpreted to mean that participants in the control arm of a trial are entitled to a “universal” standard of care.

Other international guidance documents differ. Box 5 summarizes the positions of key guidelines on the provision of health care to participants in clinical trials. Box 6 summarizes guidelines on the use of placebos in clinical research. With the exception of the Declaration of Helsinki, no

other document requires investigators to provide participants with the best standard of care available anywhere. Clearly, opinion is still widely divided on what ethics requires of clinical research. In terms of standard of care, debate is active, unresolved, and highly contentious.^{4,5}

To the extent possible, scientific rigor and benefits to study participants should not be viewed as mutually exclusive. Both can be addressed in several ways. One part of the

BOX 5: Guidelines on Required Provision of Health Care for Participants in Clinical Trials

Declaration of Helsinki

- No specific mention of HIV prevention trials.
- No specific obligations regarding provision of medical care during research.
- General statement of obligation, open to strong and weak interpretations (Paragraph 10: “It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.”)

CIOMS International Guidelines

- Guideline 21: Ethical obligation of external sponsors is to provide health-care related services.
- Must provide health-care services that are essential to the safe conduct of the research.
- External sponsors are ethically obliged to ensure the availability of treatment for subjects who suffer injury as a consequence of research interventions.

UNAIDS Vaccine Guidance Document

- Guidance Point 16: “Care and treatment for HIV/AIDS... should be provided to participants, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country in light of [circumstances specified].”

Nuffield Council on Bioethics

- Endorses Guidance Point 16 of UNAIDS Vaccine Guidance Document.
- “We conclude that where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered is the best available intervention as part of the national public health system for that disease.”
- Agreement should be reached before research begins about the standard of care to be provided to subjects.
- Any proposal for care of a lower standard must be justified to the relevant research ethics committees.

answer is close consultation with the communities involved, empowering them with tools and information to analyze and prioritize choices. Moreover, improving local standards of care may enhance the quality of research results by increasing trust and encouraging sustained participation in the trial.

Standard of care within trials: the reality

In the real versus the ideal world, determining the standard of care within trials depends on many factors—for starters, the size and budget of the trial and the availability of support from government, communities, nongovernmental organizations (NGOs), and local providers. Research projects may not be able to compensate fully for the inadequacies in local health care systems. Nevertheless, there is much that investigators *can* do: They can train health personnel, bring in new equipment, standardize care across sites, and raise awareness for services not locally available. They can assist local services to address the increased demand when previously undiagnosed health problems are identified. They should be in dialogue with the local authorities and providers, and they can make clear, up-front arrangements on the provision of services during the study. Similarly, they can support community advocacy to demand that the government improve and expand the provision of services.

In reality, the concept of a universal “fixed” standard can be problematic. Contexts vary, and something that may be feasible or optimal in one place may be inappropriate

or undoable in another. Furthermore, the “state of the art” constantly changes. The expected standard of care may no longer be right by the time the trial has been underway for some time.

Participants endorsed the view that sponsors should improve the local standard of care available during the conduct of research trials. The goal should be to move toward state-of-the-art care in the long run while doing as much as possible in the meantime. South African ethicist Solomon Benatar first advanced this notion, which he referred to as “ratcheting up” the standard of care. As Shapiro and Benatar observe:

[Standard of Care] should include several interlinking features that would promote fairer distribution of burdens and benefits in both short and long term for participants in communities. First, research should be undertaken in the best interests of trial participants by involving them in decisions around research design and implementation. Second, the dignity of participants should be respected, wherever they are in the world. Third, consideration should be given to the broader community benefit that could be achieved by raising the standard of health care through partnerships created by the research endeavor. That the ideal of first world health care cannot be achieved immediately in developing countries should not be a deterrent to efforts to raise existing levels of care. By setting high ideals and working towards, them, the standard of care could be progressively ratcheted upwards.⁶



⁴ Lie RK, Emanuel E, Grady C, Wendler D. The standard of care debate: the Declaration of Helsinki versus the international consensus opinion. *Journal of Medical Ethics*. 2004; 30:190–193.

⁵ Schüklenk U. The standard of care debate: against the myth of an “international consensus opinion”. *Journal of Medical Ethics* 2004;30:194–197.

⁶ Shapiro K, and Benatar SR. HIV Prevention Research and Global Inequality: Steps Towards Improved Standards of Care. *Journal of Medical Ethics*. 2005;31:39–47.



BOX 6: Guidance Related to Use of Placebos in Clinical Trials

Declaration of Helsinki

- Paragraph 29: “The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.”

CIOMS International Guidelines

- Guideline 11: “As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or no treatment.”
- A placebo may be used (i) when there is no established effective intervention; (ii) when withholding an established effective intervention would expose the subjects to, at most, temporary discomfort or delay in relief of symptoms; (iii) when use of an established effective intervention as comparator would not yield scientifically reliable results and use of a placebo would not add any risk of serious or irreversible harm to the subjects.
- Commentary of Guideline 11: “An exception to the general rule is applicable in some studies designed to develop a therapeutic, preventive, or diagnostic intervention for use in a country or community in which an established effective intervention is not available and unlikely in the foreseeable future to become available, usually for economic or logistic reasons. The purpose of such a study is to make available to the population of the country or community an effective alternative to an established effective intervention that is locally unavailable.”

Nuffield Council

- Wherever appropriate, participants in the control group should be offered a universal standard of care for the disease being studied. Where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered to the control group is the best intervention available for that disease as part of the public health system.

Council of Europe

- Article 23.2: “Research shall not deprive participants of necessary procedures... In research associated with prevention, diagnosis, or treatment, participants assigned to control groups shall be assured of proven methods of prevention, diagnosis or treatment.”
- “It is expected that a proven method of treatment that is available in the country or region concerned be utilized.”

National Bioethics Advisory Commission Report

- Researchers and sponsors should design clinical trials that provide members of any control group with an established effective treatment, whether or not such treatment is available in the host country. Any study that would not provide the control group with an established effective treatment should include a justification for using an alternative design. Ethics review committees must assess the justification provided, including the risks to participants, and the overall ethical acceptability of the research design.

European Group on Ethics in Science and New Technologies

- Opinion #17: The use of placebos should be regulated in developing countries in principle by the same rules as in European countries. Any exception must be justified: an obvious one is when the primary goal of the clinical trial is to try to simplify or to decrease the costs of treatment for countries where the standard treatment is not available for logistic reasons or inaccessible because of cost. It may thus be justified to derogate from the rule of best-proven treatment. The justification of using a placebo must be clearly demonstrated in the research protocol submitted to the ethical committees and especially approved by the local committee.
- It should be noted that two members of the group recorded their consent, noting “Use of a placebo to develop a low cost treatment could mean accepting a ‘double standard’ for rich and poor countries.”

UNAIDS Guidance for Preventive HIV Vaccines

- Participants in the control arm of a future Phase 3 HIV preventive vaccine trial should receive an HIV vaccine known to be safe and effective when such is available, unless there are compelling scientific reasons which justify the use of a placebo.

In short, establishing appropriate standards of care is a process. Research endeavors should leave participants and their communities better off after the trial, not merely “not worse off.” To achieve this goal requires persistence, creativity, and the capacity to act in partnerships.

From principles to protocol

Even when there is a consensus that care should be improved, actually making and incorporating health care decisions into a trial protocol is still difficult.

Investigators face hundreds of concrete decisions about individual aspects of care: Should contraceptives be provided directly by the trial or can participants get adequate care from local family planning clinics? What if a pelvic exam indicates that a woman has cervical cancer and no local treatment is available? Should viral load and CD4 tests be done for women who are HIV positive at screening?

The ethics document of the HIV Prevention Trials Network (HPTN)⁷ suggests that investigators categorize three groups of care: first, the services offered to participants to help them remain HIV negative (that is, the prevention package); second, the services integral to the conduct of the trial (for example, HIV and pregnancy testing); and third, health or other benefits beyond those required to evaluate the study endpoint.

Study teams should next consider the pros and cons of particular elements of care in each of these three categories. They need to consider the possibility of alleviating suffering (narrowly or broadly), reducing (or exacerbating) inequities, creating ethical inducements (or unfair pressure) to participate, and contributing to (or undermining) the sustainability of care. Researchers can analyze these elements in consultation with key stakeholders and community members. Together, they should work to define and decide upon the



⁷ See Chapter 3, Table 4 for a summary of key guidance documents.



appropriate package of care. This includes consideration of unintended consequences and ways to sustain or reduce the negative impact of care ceasing at the trial's end. Some real-life challenges faced by investigators in HIV prevention trials are explored in Box 7.

Participants agreed that services provided within the study—at the very least—should be better than the local standard of care. If the “best proven” standard of care is not to be provided, the rationale should be set forth in writing, with neither expediency nor expense alone constituting adequate justification.

The practical advantages of providing improved care to the entire community—not just to those enrolled in the study—were also recognized. This reduces reinfection rates and promotes sharing of benefits, for example, through improved STD treatment. It also avoids concerns about generating undue inducement to enroll. One suggestion was to aim for a sustainable standard of care for the whole community that is as good as or better than that defined by government health policy. Where such policies exist, they often dictate standards of care that are better than what is available locally, thus reinforcing the importance of implementing policies and

BOX 7: Challenges in Standard of Care: A Survey by the HIV Prevention Trials Network

In 2003, the HIV Prevention Trials Network (HPTN) carried out an email survey of standard of care at ten trial sites. The purpose was to learn about care currently provided, care available at the same facilities but outside the research, and care accessible through referrals.

In general, the services available to the general population (either free or for a fee) were found to be more limited than those available to research participants. The trial participants received fairly comprehensive HIV prevention services, including voluntary counseling and testing (VCT), as well as male condom distribution and counseling. Antiretroviral treatment (ART) was not offered in the trial benefits package at the ten sites surveyed. However, ART was available in the same facilities at a subsidized cost in three of the locales. At three sites, trial participants were offered treatment of opportunistic infections. Four sites provided two-dose nevirapine to pregnant women for prevention of mother-to-child transmission. However, no sites offered breast milk substitutes, and only two made referrals for substitutes.

In general, reproductive health services offered to trial participants tended to be minimal or nonexistent, though all women in microbicide trials could arguably benefit from access to family planning or obstetrical services as part of study follow-up, regardless of their HIV status.

Three of the nine sites also provided female condoms to participants. This raises a new question, illustrating the difficulties in establishing standards for research participants' care. Among experts, interpretations differ on the evidence base for the effectiveness of female condoms. So, should female condoms be included as part of a standard prevention package?

The HPTN assessment serves as a reminder of the challenges that researchers face in attempting to ensure appropriate standards of care for women in microbicide trials. The results helped HPTN to identify areas where referrals needed to be strengthened and other steps to improve access to care and treatment for planned microbicide trials. It should be noted that access to HIV treatment and care has improved significantly at some sites since the survey was completed as a result of global efforts to scale up treatment access.

programs to the public health system. Together with local officials, researchers should advocate that governments sustain these services when the trial ends.

Still unresolved is the question of whether higher standards should be set for international research sponsored by outside parties, versus locally initiated research. Requiring the “best proven” standard of care for all research studies could dramatically undermine the capacity of local investigators to pursue relevant research. The question is whether a local investigator, who may not have the means to provide the best proven treatment, can nonetheless proceed while still expecting industry-sponsored researchers to provide “best proven” treatment in their trials. A number of participants argued that while standard of care for locally initiated, low-budget research could be lessened, international and pharmaceutically sponsored research should be held to the highest possible standards, lest flexibility be interpreted to mean that anything better than local care is appropriate, even by those with the resources to provide more.

Microbicides, placebos, and the investigator’s dilemma

All ongoing microbicide trials provide free access to condoms and state-of-the-art counseling on risk reduction. They also provide STD testing and treatment (some treat only symptomatic STDs whereas others routinely screen for STDs using high-end diagnostics). These interventions are known to reduce HIV transmission; so current vaccine and microbicide trials do *not* have a classic “no-treatment arm.” They do, however, use placebos for “blinding”

purposes, that is, to keep both participants and research staff from knowing which group received the active microbicide.

Significantly, both the microbicide and vaccine fields have rejected classic placebo-controlled trials. Although the quickest and most “efficient” microbicide trial would theoretically be to compare a candidate microbicide with a placebo microbicide without offering condoms and STD treatment, this scenario has been widely rejected as unethical.

Evidence demonstrates, however, that even with access to condoms and extensive risk-reduction counseling, women nonetheless experience significant rates of HIV infection, even those who are enrolled in prevention trials.⁸ It is precisely the fact that many women cannot use condoms that makes the search for a new prevention tool so urgent. The consequence of this reality is that microbicide studies *are* able to evaluate the effectiveness of candidate products, even though condoms are available and actively encouraged, and STD treatment is provided.

That said, reducing the incidence of HIV infection in a study population does diminish the statistical power of the study in the sense that it becomes more difficult to demonstrate the efficacy of a microbicide. Therefore, researchers may have—or at least be perceived to have—a disincentive to rigorously promote the use of condoms and other risk-reduction interventions. This so-called investigator’s dilemma has long been acknowledged and extensively discussed within the microbicide community.⁹ Most study nurses, counselors, and staff are fully committed to the health and well-being of



⁸ Bartholow B, Buchbinder S, Celem C, et. al. HIV risk behavior over 36 months of follow up in the world’s first HIV vaccine efficacy trial. *Journal of Acquired Immune Deficiency Syndrome*. 2005; 39(1): 90–101.

⁹ DeZoysa I, Elias C, Bentley M. Ethical challenges in efficacy trials of vaginal microbicides for HIV Prevention. *American Journal of Public Health*. 1997; 88(4):571–575.



participants during the trial. They understand their clear responsibility to help participants reduce their HIV risk. However, to minimize both real and perceived conflict of interest, participants in the 1997 ethics consultation recommended that investigators consider enlisting a separate entity to conduct the trial's risk-reduction counseling. This practice helps to address concerns that the rights of participants could conflict with research goals.

Yet similar questions remain. What if interventions other than condoms and STD

treatment are shown to reduce risk—for example, male circumcision, herpes treatment, or a novel microbicide? Should these interventions become part of the mandatory package of prevention services offered to participants in HIV prevention trials? Should experimental interventions be included in the standard of care in future prevention trials, even if not fully accepted as standard practice in HIV prevention programs? These questions are explored in greater depth in Chapter 9, "Testing Second-Generation Microbicides."