Chapter Two

Ethical Considerations in the Design and Conduct of International Clinical Trials

Introduction

As we stand poised on the frontiers of biomedical science, populations worldwide face a broad range of health concerns as well as many different issues related to the conduct of clinical trials in international health research. The multiple contexts within which biomedical research proceeds call for an array of research designs in order to forge scientific developments and advance clinical knowledge and treatment approaches. Any of a number of research designs may be appropriate for a clinical trial, depending on the context and circumstances of the research; however, every clinical trial must be scientifically sound and must incorporate important ethical principles regarding the treatment of research participants.

With respect to the ethical treatment of research participants, current U.S. regulations require that Institutional Review Boards (IRBs) determine that a research design is such that "risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result" (45 CFR 46.111(a)(2)). However, although the federal regulations do not require IRBs to review the scientific merit of a research design, research with a scientifically flawed methodology will not generate valid or reliable data or produce generalizable and beneficial knowledge. In such cases, it is the participants in the research who will incur the risks, inconveniences, or discomforts that might be involved. Because it would be wrong to put people at risk or even to inconvenience or discomfort them through participation in a poorly designed study, the scientific merit of research becomes an ethical issue (OPRR 1993). Therefore, the National Bioethics Advisory Commission (NBAC) believes that IRBs should assure themselves of both the ethical *and* scientific merits of the protocols they review. The Commission is not proposing that IRBs become responsible for conducting scientific peer review (as they may lack specific expertise, and in most instances the proposed studies of research sponsors must undergo independent scientific review)—but only that IRBs have confidence that a study has scientific merit.[1]

Even when a clinical trial uses a scientifically sound research design and addresses important questions, conducting the proposed research might be unethical if it would result in the violation of certain ethical principles. However, because determining the appropriate design for a clinical trial depends on various contextual considerations, what might be an ethically acceptable design in one situation could be problematic in another. For example, it might be unethical to conduct a clinical trial for a health condition in a country where that condition is unlikely to be found, but the same trial might be appropriately conducted where the results could be important to the local population. A more challenging question is whether a research design that could *not* be ethically implemented in the sponsoring country could be ethically justified in a host country when the health problem that the research is addressing is common to both countries.

It may be useful to classify international collaborative research projects in developed and developing countries on a continuum. At one end of the continuum is research that has no practical relevance to the health needs of the host country, but is important to the foreign sponsor or researcher. At the other end of the spectrum is research that is directly relevant to the health concerns of the host country, but not to sponsors or researchers. These two

extremes illustrate how situations can differ starkly, particularly regarding the potential for exploiting research participants in the host country. An assessment of the ethical appropriateness of a particular study's design should include an evaluation of where it lies along this continuum. It is worth noting that in an NBAC survey of U.S. researchers, 40 percent of those surveyed said that the research priorities of their funding agencies were incongruent with the top priorities of the developing country in which they were conducting research. Indeed, the relevance of the proposed research to the host country was questioned by U.S. IRBs in 30 percent of the cases reported and by host country ethics review committees in 23 percent of the cases. At the same time, a majority (73 percent) of U.S. researchers surveyed said that their interest in addressing global inequalities in health motivated them to work in a developing country.[2]

This chapter focuses on the ethical requirement of choosing a research design that minimizes the risk of harm to human participants in clinical trials and that does not exploit them (which raises the question of the obligations of sponsors and researchers to the research participants *during* the trial). Chapter 4 discusses the broader question of what obligation, if any, sponsors and researchers have to the participants and others in a host country *after* a research trial is completed. Following are some of the chief considerations with respect to both research design and ethical obligations owed to research participants:

- whether the research is responsive to the health needs of the host country;
- whether a study design is appropriate for answering the primary research question;
- whether an effective treatment already exists for the condition that is the focus of the study;
- whether the condition for which a new intervention is sought is severe or life threatening;
- the probability and magnitude of any harm that might come to participants in both the experimental and control arms of a given study;
- the probability and magnitude of benefits that may accrue to the study participants;
- the balance of the risks to the participants and the probable benefits to the participants and to others; and
- the future availability of the experimental intervention, if proven effective, to participants and others in the host country after the trial.

Because the choice of a study design for any particular trial depends on these and other factors, it would be inappropriate—indeed, wrong—to designate any one particular study design as ethical for all research situations. Nevertheless, under certain specified conditions, a particular design can be considered ethically preferable.

> ***Recommendation 2.1:*** **Researchers should provide ethics review committees with a thorough justification of the research design to be used, including the procedures to be used to minimize risks to participants.**

Ethical Issues in Clinical Trial Design

Important and distinct scientific and ethical issues and challenges can arise at different stages of drug development, during the development of other medical interventions, and in the use of various study designs used for clinical trials. The development of a new drug is a long and complex process that includes drug discovery, preclinical testing, and, finally, an ordered program of clinical trials. The development of other medical interventions—such as new vaccines, gene transfer technology, and medical devices—follows a similar process. Exhibit 2.1 summarizes the phases of drug development that typically form the basis of U.S. efforts. Exhibit 2.2 describes the principal types of trial designs used in testing clinical interventions.

Carefully designed and properly conducted clinical trials are recognized as the principal mechanism for testing new clinical interventions, and, given the rapid advance of biomedical science in recent years, the number of clinical trials is steadily increasing. The results of any clinical trial must be free of bias, which can be caused by flaws in the study design. Bias in clinical trials refers to the tendency of any aspect of the methodology or the interpretation of data to lead to conclusions about

Exhibit 2.1: Phases of Drug Development

The first step in the development process of a new drug, biologic (e.g., a vaccine, a gene transfer agent, a protein-based therapy), or medical device is called *discovery*. During the drug discovery process, chemical compounds are identified and/or synthesized and tested for biological activity. Of 5,000 to 10,000 chemical compounds tested for biological activity, approximately 250 eventually enter the next stage of drug development, called *preclinical testing* (PhRMA 1999).

Preclinical studies are experiments that are carried out in the laboratory and in animals to provide preliminary evidence that the experimental intervention will be safe and effective in humans. Safety information from preclinical testing is used to support a request to the Food and Drug Administration (FDA) to begin testing the experimental intervention in humans. Preclinical testing usually takes three to six years, and only 2 percent of compounds evaluated in preclinical testing are eventually tested in humans (Mann 1999; PhRMA 1999).

In the United States, an investigational new drug (IND) application or an investigational device exemption (IDE) must be submitted to the FDA before a drug, biologic, or device can be studied in humans. Once the FDA allows an IND or IDE to proceed, testing of an experimental intervention in a clinical trial can begin. For studies conducted outside the United States, an IND is not required, unless data from the study are intended to be used to support the licensing of a drug in the United States. Clinical trials usually are classified into the following four phases: *Phase I trials*, the earliest-stage clinical trials for studying an experimental intervention in humans, are small (typically fewer than 100 participants) and aim to determine the toxicity and maximum safe dose of a new drug. Phase I trials commonly are conducted with normal volunteers (rather than patients with the condition in question). However, Phase I trials that involve potent and potentially toxic chemicals (e.g., for cancer or HIV/AIDS) are often performed in participants with advanced disease who have not responded to all other standard treatments.

Phase II trials usually involve 100 to 300 participants and are designed to determine whether a drug produces any clinically significant effects in those with the targeted disease. If the results of these trials are promising, then a larger *Phase III trial*, aimed at establishing efficacy, may be conducted. Phase III trials are large, frequently multi-institution studies, and typically involve from a hundred to thousands of participants. Approximately 25 percent of all drugs tested in clinical trials successfully complete Phase III testing (Mann 1999).

Some Phase II and Phase III trials are designed to be *pivotal trials* (sometimes also called confirmatory trials). The goal of a pivotal trial is to eliminate systematic biases and increase statistical power and to establish the intervention's safety and efficacy. By providing firm evidence of safety and efficacy, pivotal trials are designed to produce data that will be accepted by the FDA as adequate for supporting a New Drug Application (NDA). On average, it takes almost seven years to complete the required clinical trials (Phases I through III) and to gather the data necessary to establish the safety and efficacy of an experimental intervention (PhRMA 1999).

Once sufficient evidence exists regarding the safety and efficacy of an experimental intervention from studies conducted inside and/or outside the United States, an NDA is submitted to the FDA for approval of a new drug; a Biologic License Application is submitted for approval of a new vaccine or other biologic; or a Product License Application is submitted for approval of a new device. Occasionally, the FDA requires *Phase IV trials*, which are usually performed after the intervention has been approved. Such post-marketing surveillance aims to obtain additional information about the risks, benefits, and optimal use of the intervention by observing the results of the intervention in a large number of patients. Phase IV trials enable the long-term effects of an intervention to be assessed and sometimes reveal rare, but serious, side effects.

the effects of an intervention that are systematically different from the truth (FDA 1999). Ensuring that the chosen study design avoids various forms of bias and generates data that can answer the scientific questions being asked can be difficult. Fortunately, a significant literature has been developed to address this challenge (Meinert and Tonascia 1986; Sackett 1983; Spilker 1991).

From the perspective of the protection of human participants in research, one of the most critical issues in clinical trial design concerns the use and treatment of control groups, which are often an essential component in methodologies used to guard against bias. The main purpose of a control group is to permit investigators to determine whether an observed effect truly is caused by the experimental intervention being tested or whether it

Exhibit 2.2: Clinical Trial Designs

Clinical trials are research studies that evaluate new ways to prevent, detect, diagnose, or treat disease in human beings. The key to clinical trial design is choosing an approach that addresses the scientific question being asked, the intervention being tested, and the group of participants involved, while at the same time considering the risks and benefits to the participants. Several commonly used research designs include the following:

Add-on design: A placebo-controlled trial of an experimental intervention is tested in people who are already receiving an established effective treatment.

Crossover design: Each participant is randomized to a sequence of two or more treatments and hence acts as his/her own control for treatment comparisons.

Equivalence trials: 1) compare the efficacy of an experimental treatment to that of an established effective treatment (also called noninferiority trials) and 2) compare bioequivalence (to show that two drugs have the same potency and tissue availability).

Factorial design: Two or more treatments are evaluated simultaneously in the same participant population through the use of varying combinations of the treatments (e.g., in a 2 x 2 factorial design, participants are randomly allocated to one of the four possible combinations of two treatments: A alone, B alone, both A and B, neither A nor B).

Group sequential design: Allows the trial to be monitored at specific time intervals so that a treatment arm, or the entire trial, may be stopped early if there is clear evidence of efficacy or of unacceptable adverse effects.

Parallel group design: Participants are randomized to one of two or more arms, and each arm is allocated a different treatment.

Randomized withdrawal design: Participants who respond positively to an experimental intervention are randomized either to continue receiving the intervention or to receive a placebo.

Superiority trials: Trials designed to determine whether an experimental intervention is more efficacious than an established effective treatment.

is caused by other factors, such as the natural progression of the disease, observer or participant expectations, differences in the baseline condition of subjects, or other treatment (FDA 1999). The experience of an appropriately selected control group lets the investigator know what would have happened to study participants had they not received the test intervention or what would have happened had they received a different treatment that is known to be effective (FDA 1999). (A description of and additional discussion regarding the use of control groups is provided below.)

This chapter will discuss the following ethical issues involved in evaluating any proposed clinical trial: equipoise; randomization; the nature and treatment of control groups; the distinction between efficacy and effectiveness studies; and the selection of the participant population and sample size.

Equipoise

Among the most important ethical and scientific justifications for beginning a clinical trial is the uncertainty about whether the experimental intervention is better than the status quo (which may be an existing treatment or no treatment at all). This state of uncertainty is known as *equipoise*, and it is a requirement for the ethical conduct of a clinical trial. Equipoise has been defined as the point at which a rational, informed person would have no preference between two (or more) available treatments (Lilford and Jackson 1995). It is a state in which honest professional disagreement exists among experts regarding whether the study intervention or the control is preferred. In the *clinical context*, the belief that one intervention is superior to others ethically compels the clinician to recommend the superior intervention. Clinicians are justified in recommending different treatments based on their assessment of what will be effective for a particular patient. Often, the preferences of a clinician regarding an intervention and those of the patient are similar in this regard. However, in the *research context*, individual preferences are replaced by the collective uncertainty of the clinical community. According to this concept of *clinical equipoise*, a trial is ethical if there is "genuine uncertainty within the expert medical community about the preferred treatment" (Freedman 1987).

It should be emphasized that often there is a considerable lack of clarity in the scientific community about the state of equipoise for a particular set of interventions. There may be no consensus about how many studies must be completed to show the efficacy of a new intervention or about how strong the evidence must be to change medical practice. In addition, there may be disagreement or concern about the applicability of research findings in, for example, different populations with different genetic backgrounds, different co-morbidities, or different environmental and social factors.[3] However, disagreements about these issues, although important, are distinct from those regarding equipoise. At the end of a clinical trial, if it is determined that an experimental intervention is superior—or inferior—to the control intervention, the state of clinical equipoise may have been eliminated or evidence may have been accumulated that could lead to such a conclusion. Therefore, although a clinical trial starts in a state of equipoise, investigators hope that the analysis of the data collected during the trial will remove or reduce the level of uncertainty.

Randomization

Randomization is the process by which participants in a clinical trial are assigned to different interventions in a study. Through randomization, each person has a specified chance of being assigned to one or another group. Randomization differs from systematic assignment, in which individuals are assigned to a particular arm of a study for a specific clinical, scientific, or perhaps demographic reason (e.g., medical history, presence of a genetic marker, age). Rather, it is a process used to minimize any inherent differences among participants in the various arms of a trial by distributing people with particular characteristics randomly to the intervention and control arms, and it is the only way to equalize all factors, known and unknown, between study groups (Fletcher et al. 1982). The consensus among clinical investigators is that nonrandomized controls can create severe bias and therefore may result in unreliable trial results. Along with the use of placebos (defined as an intervention that although physically resembling the intervention being tested is inert and not expected to have any pharmacological effect on the condition being treated) or other controls as well as double blinding (in which neither the investigator nor the participant knows which intervention, if any, the participant is receiving), randomization of a study is essential in evaluating new interventions. At times, however, randomized trials are not practical, such as when an insufficient number of participants is available to provide the statistical power needed for drawing conclusions.[4]

Types of Control Groups

The first documented example of a controlled clinical trial was James Lind's experiment in 1747 with 12 sailors with scurvy aboard the *H.M.S. Salisbury* (Lind 1753). Lind divided the sailors into six groups of two each and compared the effects of providing different nutritional supplements to each group. The two men who ate oranges and lemons recovered immediately. Lind concluded that something in the citrus fruit was counteracting the cause of the scurvy, so he gave citrus fruit to all the other men and observed that they too were cured of the disease. Lind's experiment laid the initial groundwork that established the controlled clinical trial as the best method for determining the effects of new therapies.

The FDA classifies clinical trial control groups into five types: placebo concurrent control, active treatment concurrent control, no treatment concurrent control, dose-comparison concurrent control, and external control (FDA 1999). Each type has strengths and weaknesses, depending on the scientific question being asked, the intervention being tested, and the group of participants involved. Therefore, because no one type of control group is ideal in all situations, researchers should choose the one that best answers the scientific question to be addressed and presents the least risk to the participants. Because of their importance, placebo concurrent control and active treatment concurrent control trials are described more fully below.

Placebo Concurrent Control

A placebo is an intervention that physically resembles the intervention being tested, but is inert and not expected to have any pharmacological effect on the condition being treated. Placebo-controlled trials control not only for the *placebo effect* (changes in a person's physical

or mental condition that result from his or her belief that the study is providing an active treatment), but also for changes that arise due to the natural course of the disease; participant or investigator expectations; the use of other therapies; and the subjective elements of a diagnosis or assessment (FDA 1999). By including a placebo group in a clinical trial, the action of the experimental intervention can be distinguished from other confounding factors and from changes that can be attributed purely to the physical or socioeconomic environment.

For some clinical trials, the decision regarding the appropriateness of using a placebo is not problematic. It is generally accepted that when no established intervention exists to treat or prevent the condition being studied, it is ethically acceptable to give the control group a placebo. This is because in such trials, there is no treatment against which to compare the experimental intervention. Another argument in favor of the use of placebo controls has been made in the context of research conducted in a developing country. Many researchers have contended that the research question must be defined differently in a setting in which health care resources are limited and participants do not have access to established effective treatments outside of the research context. Some have advocated that in these cases, the measurement of absolute efficacy of a new and potentially more affordable and available intervention is a more relevant research question for the host country than the comparison of a new intervention to an established effective treatment already available elsewhere (Levine 1999; Perinatal HIV Intervention Research in Developing Countries Workshop Participants 1999).

On the other hand, virtually all experts believe that a placebo-controlled trial would not be ethical if an established effective treatment that is known to prevent serious harm—such as death or irreversible injury—is available and can be provided. NBAC agrees with the consensus that it is not ethically acceptable to perform placebo-controlled clinical trials when established effective treatments exist (such as in the cases of new thrombolytics [blood clot-dissolving agents], beta blockers, aspirin, or angiotensin-converting enzyme inhibitors to improve survival after heart attacks, or new chemotherapeutics for leukemia or testicular cancer).[5] Even under these circumstances, however, exceptions may exist if an established effective treatment does not work in certain populations or has such serious side effects that some patients refuse treatment.

In the United States, there is substantial agreement in the research community that the use of placebos in studies involving severe or life-threatening illnesses when existing treatment could prevent them or delay their progression is ethically suspect.[6] The American Medical Association's (AMA's) guidance for the use of placebos states that "protocols that involve conditions causing death or irreversible damage cannot ethically employ a placebo control if alternative treatment would prevent or slow the illness progression….In general, the more severe the consequences and symptoms of the illness under study, the more difficult it will be to justify the use of a placebo control when alternative therapy exists" (AMA 1999). In contrast, most experts agree that the use of a placebo is acceptable if it does not harm the participants and only results in discomfort (Temple 1996). Similarly, guidance from the International Conference on Harmonisation (ICH) indicated that with informed consent and appropriate review by an IRB, research participants could be asked to participate in placebo-controlled trials, even if an existing treatment is available, when the only risk from not receiving treatment is discomfort (ICH 1996). In such cases, it is necessary to ensure that the setting is not coercive and that the participants are fully informed about other available therapies and the consequences of delaying treatment (FDA 1999).

Ethics review committees will rightfully exercise their judgment in assessing research designs that employ a placebo control. However, the Commission believes that there are some studies for which the presumption in favor of active controls simply cannot be overcome. Although NBAC did not review the protocol, it appears that a recently reported case may serve as example of such a study (see Exhibit 2.3). In addition, as reflected in the recommendations in this report, the study discussed in the exhibit would be unacceptable because it intends to use developing country citizens as research participants while its primary purpose is to develop a drug for market in the United States and other developed countries.

Exhibit 2.3: Placebo Versus Established Effective Treatment (Active Control)

In early 2001, a proposal was submitted to the FDA by a U.S. biotechnology company for approval of a three-arm study of a new surfactant drug in as many as four Latin American countries. In the study, a control group of premature newborn infants with Respiratory Distress Syndrome (RDS)—a potentially fatal condition—would be treated with placebos, rather than a life-saving and already FDA-approved surfactant drug (Flaherty and Stephens 2001; Lurie et al. 2001). The apparent justification for conducting these studies is to decrease the time needed to develop the drug, which is intended for market in the United States. The company also plans to conduct a similar study on newborns in Europe, where no placebo controls will be used. Instead, all newborns will receive either the experimental intervention or another already approved surfactant.

Concerns have been voiced about whether the proposed study is ethical, mainly because the study design involves the use of a placebo control when an established effective treatment exists (Flaherty and Stephens 2001; Lurie et al. 2001). Thus, approval is being sought to conduct research in a developing country that could not be ethically justified in a developed country. Indeed, internal FDA documents state that "conduct of a placebo controlled surfactant trial for premature infants with RDS is considered unethical in the USA" (Lurie et al. 2001). The company, however, contends that because infants in Latin America with RDS who do not have access to established drugs would not be left worse off by placebo treatment, the proposed study is ethically justifiable in the hospitals where surfactant drugs are not available (Flaherty and Stephens 2001; Lurie et al. 2001). It is widely accepted, though, that in cases such as RDS that involve a life-threatening condition, a placebo control should not be employed when an established effective treatment exists against which the experimental intervention can be tested.

The other ethical concern that has been raised about the proposed study is that poor Latin American newborns would be participating in testing an intervention, which, if proven effective, would be too expensive for their families or others in the host country (Flaherty and Stephens 2001; Lurie et al. 2001). The company has indicated that, to some extent, it will provide the drug at a reduced cost to the host countries if it is proven effective (Flaherty and Stephens 2001; Lurie et al. 2001). Nevertheless, the lack of care available in a developing country cannot provide the principal ethical justification for using such a research design, especially when the benefits of the study are intended primarily for the developed world.

In studies of this kind—in which the disease is life threatening, an established effective treatment is available, patients in developed countries will be the primary beneficiaries of the results of the clinical trial, and it is not clear that the clinical trial is responsive to the health needs of the host country—a placebo control would not be permissible under the rules recommended in this report.

Yet, there are some who criticize the use of placebo controls even in cases in which risks to participants are low. One argument against the use of placebos is often grounded in the *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, which states that "[i]n any medical study every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method" (WMA 1964, as amended in 1989). Giving research participants a placebo in place of an established effective treatment deprives them of the "best proven diagnostic and therapeutic method" (WMA 1964, as amended in 1989). Moreover, some critics argue that 1) research participants should not face unnecessary pain or disease resulting from a medical experiment (Rothman and Michels 1994); 2) using a placebo instead of an established effective treatment knowingly breaches researchers' duty to minimize harm (Levine 1998); and 3) it is unethical for individual investigators to enroll patients in a study in which some participants are expected to do even slightly worse than others (Barinaga 1988).

Indeed, although the placebo-controlled, randomized, double-blind clinical trial is an authoritative and widely accepted standard for new drug evaluation, some have argued that it is not always ethical to use this trial design (Freedman et al. 1996). In situations in which the best scientific design is not ethically acceptable, it may be necessary to reconsider the primary research question and to choose one for which an ethically acceptable design can be proposed (Levine 1998), or it may be necessary to accept the fact that ethical constraints can create limitations to obtaining scientific knowledge.[7]

The recent revision of the *Declaration of Helsinki* attempts to resolve the debate about placebos by recommending that "[t]he benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists" (WMA 1964, as amended in 2000). Certain criticisms about this provision remain—principally that it makes it very difficult, if not impossible, to conduct placebo-controlled trials when such trials may be the only method of addressing the health needs of a particular population (Enserink 2000).

Active Treatment Concurrent Control

Although placebos are a frequently used control for clinical trials, it is increasingly commonplace to compare an experimental intervention to an existing established effective treatment. These types of studies are called *active-control* (or positive control) *studies*, which can take two forms—*a superiority trial*, in which the question is whether the new drug will be superior to the active control, and an *equivalence* (noninferiority) *trial*, in which the question is whether the new drug will be equivalent to but not inferior to the active control (Hauck and Anderson 1999). Active-controlled trials are often extremely useful in cases in which it would be unethical to give participants a placebo because doing so would pose undue risk to their health or well-being.

In an active-control study, participants are randomly assigned to the experimental intervention or to an active-control treatment. Such trials are often double blinded, but this is not always possible. Many oncology studies are considered impossible to blind because of the variable regimens, different routes of administration, and range of toxicities involved. In a study in which an active control is used, it may be difficult to determine whether the active control or the experimental intervention had an effect unless the effects of the treatments are obvious or a placebo control is included. For example, because the natural history of depression varies from patient to patient and it is often difficult to prove that a standard treatment has had an effect, studies of anti-depressants usually include both an active control and a placebo control.[8]

Treatment of Control Groups

Within the context of active treatment concurrent controls, it is useful to consider whether, and if so under what circumstances, researchers and sponsors are obligated to provide an established effective treatment to the control group, even if that treatment is not available in the host country. In the survey conducted by Nancy Kass and Adnan Hyder, more than half (52 percent) of the surveyed U.S. researchers conducting studies with control groups in developing countries thought that the standard of care in the host country was lower than that in the funding country. This created ethical difficulties in establishing appropriate procedures for the control group. A strong majority (78 percent) of these researchers believed that the level of medical care provided to control groups should be decided on a case-by-case basis.[9]

One view pertinent to this dilemma was expressed to the Commission in the following way: It is unethical to provide members of a control group with an established effective treatment if that treatment is unavailable in the country where the research is conducted. This is because the opportunity to obtain this treatment would render the choice to enroll in the study irresistible, as those receiving the treatment are unlikely to be able to get it once the trial is over.[10] The Commission does not agree with this proposition, because cases exist in which trials using the established effective treatment as a control would generate valuable information that is responsive to the health needs of the host country.

Some might argue that researchers and sponsors are under no ethical obligation to provide members of a control group with an established effective treatment if that treatment is unavailable in the country in which the research is conducted. This position maintains that the researchers' and sponsors' obligations to participants do not go beyond providing treatments that are routinely available to the majority of people in the host country.

Still others might contend that researchers and sponsors have an obligation to provide members of a control group with an established effective treatment even if that treatment is unavailable in the host country. Supporters

of this view assert that a special relationship is created when sponsors and investigators from a developed country enter a developing country to conduct research. For many, these obligations arise regardless of the prevailing situation in a particular location or country.

A description of the obligations that arise from these situations can be found in the basic principles of research ethics presented in the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (National Commission 1979) and many other national and international guidelines. For example, the most straightforward interpretation of the principle of beneficence—to "maximize possible benefits and minimize possible harms"—is that sponsors and investigators should make an established effective treatment available whether or not it is routinely available, because providing the treatment to the control group would maximize possible benefits and minimize possible harms to that group. Therefore, assuming that the sponsoring agency or organization can provide an established effective treatment and that the host country's collaborators, ethics review committee, and ministry of health or other appropriate authority are willing to accept the established effective treatment as part of a randomized controlled trial, a presumption should exist to provide members of a control group with an established effective treatment whether or not that treatment is available in the host country.

A tension exists, however, between this version of the principle of beneficence and the need for a research design that is relevant to real health concerns facing the population of the host country. These concerns may not be the relative efficacy of the new intervention (compared to the established treatment available in the developed countries), but rather the absolute efficacy of the intervention compared with the absence of any treatment or the level of care routinely available. Researchers in the Kass/Hyder survey described the tension between researchers' desire to benefit the larger population of the host country and their concern for the well-being of study participants. One researcher described a dramatic example of a vaccine designed to prevent children from dying from a particular tropical disease. To determine if the experimental vaccine was effective—using mortality as an endpoint—the research design entailed administering either the vaccine or a placebo to groups of children and subsequently withholding a feasible effective treatment from sick children. The researcher who described this study thought that it was imperative to develop a vaccine for this illness, but was troubled by withholding treatment that could save lives.[11]

Resolving this tension is central to the assessment conducted by ethics review committees, whose responsibilities include evaluating the ethical appropriateness of study designs. Thus, for example, in assessing a given study design, ethics review committees should consider the potential harm that may occur to participants who do not receive an established effective treatment for their condition, the strength of the evidence that a new intervention will be useful and affordable to the host country, and the feasibility of implementing an existing established treatment during the course of the study. If researchers make an acceptable case to the ethics review committee that comparing the new intervention to an established effective intervention is not a relevant research question for the host country, then the control group may receive the best care available that enables the researcher to answer a useful question.

Determining the most useful and ethical research design depends on several factors particular to the circumstances, and one can expect a certain amount of disagreement in this area. Perhaps the best answer for now is to say that investigators must carefully explain and ethics review committees must carefully scrutinize the justification for the selection of the research design, including the level of care provided to the control group. If in a proposed clinical trial the control group will receive less care than would be available under ideal circumstances, the burden on the investigator to justify the design should be heavier. Furthermore, representatives of the host country, including scientists, public officials, and persons with the condition under study, should have a strong voice in determining whether a proposed trial is appropriate. This view is reflected in certain national and international guidelines (see Appendix B) and has been advocated by others as well (Benatar and Singer 2000).

Established Effective Treatment and Best Current Methods

Chapter 1 provided NBAC's rationale for adopting the term *an established effective treatment* and indicated that this phrase refers to a treatment or a group of treatments that has achieved widespread acceptance by the medical profession (established) and that is as successful as any in treating the disease or condition anywhere in the world (effective). The treatment is not limited to what is routinely available in the host country. The Commission concluded that the standard of an established effective treatment best conveys what is owed to research participants *during* a trial.

NBAC recognizes that although it can be difficult to determine whether an intervention constitutes an established effective treatment, this term has certain advantages. Among the difficulties noted, however, was the possible disagreement of some scientists about whether an intervention shown to be effective in one population is likely to be as effective in another population that differs in significant ways. By choosing the term *an established effective treatment* and avoiding the qualifier *best*, NBAC proposes, simply, that the selection of an established effective treatment in a clinical trial conducted in a developing country must be made on a case-by-case basis.

The Commission also believes that this approach would satisfy those who have criticized the *best proven method* standard, or the established effective treatment standard proposed here, by arguing that the use of complex and very expensive medical care (such as surgery or catheterization for cardiovascular disease) in a developing country often is not feasible, even within the context of most research studies, and that such care is not sustainable after the research is complete. These commentators allege that if complex and costly medical care is used as the control against which new interventions are measured, research studies will generate data that potentially will be irrelevant to the host country—an argument analogous to that used to defend placebo use.

As noted in the discussion of placebo use, three factors must be considered by researchers when designing a study and by ethics review committees when reviewing protocols if they are to assess the level of medical care that should be provided to participants: 1) the well-being of the study participants; 2) the relevance of the research question to the host country; and 3) the feasibility of implementing a given type of medical care in the host country setting. In the case of medical treatments that involve a huge medical infrastructure or that are extremely costly to implement, feasibility may be the determining factor. In addition to feasibility, the ethical assessment of what level of care to provide often will depend on balancing the concern for the well-being of study participants with concern for the relevance of the research question to the host country. NBAC believes that researchers and ethics committees must find a balance between these important ethical demands in each research project.

> ***Recommendation 2.2:*** **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.**

Distinguishing Between Efficacy and Effectiveness Studies

Efficacy clinical trials are sometimes considered *optimal care* studies in which the research question is whether the experimental treatment works under ideal conditions. In contrast, *effectiveness* clinical trials ask whether the experimental treatment works under ordinary circumstances. Often, there are legitimate differences of opinion regarding whether an efficacy trial or an effectiveness trial is more scientifically and ethically appropriate in a given situation. On the one hand, efficacy trials ignore problems of access to care, generalizability from a highly selective sample of patients and physicians, and adherence to regimens, for example. If an efficacy trial is negative, it is hard to imagine that an effectiveness trial would show a benefit; therefore, effectiveness trials might have limited usefulness in developing countries. If an efficacy trial is productive, the question regarding

whether the intervention will be effective when used by a broader range of doctors and patients, who may not find it affordable, accessible, or acceptable, is still open. On the other hand, a problem with effectiveness trials is that if they produce a negative result, it is unclear whether the experimental intervention would fail under any circumstances, or only because patients and doctors lacked access to it, or because the doctors were unskilled or the patients poorly adherent.

In an efficacy trial, the control group should receive the best established treatment. However, in an effectiveness trial, the research question cannot always be answered by giving the control group the best established treatment. No consensus has emerged that the research questions posed in efficacy trials would be as pertinent to the needs of a host country as would the research questions posed in effectiveness trials. To provide the best established treatment would be to ask a completely different research question, one that may not be relevant to the clinical needs of the population being studied.

Another consideration in the context of developing country research is that a new intervention's degree of effectiveness may be critically important in terms of allocating scarce resources. Although a new intervention may be shown to be significantly better than existing or no treatment, policymakers may want to determine exactly how much benefit can be derived from the new intervention before deciding to allocate funds to implement it, particularly when there are competing health priorities in the host country.[12]

Selection of the Participant Population and Sample Size

Another important study design issue is the selection of the population to be studied. In the early phases of drug development, for example, research participants are selected from a small subgroup of the patient population in which the drug eventually may be used (CPMP 1995). This is done to maximize the opportunity to observe specific clinical effects of interest. By the time the experimental intervention enters pivotal Phase III trials, the participants should more closely mirror the intended users. Therefore, in these trials the criteria for selecting participants usually are relaxed as much as possible, without jeopardizing the possibility of conducting a successful trial. However, even a Phase III clinical trial usually is not completely representative of future users, because of several factors, including the geographical location of the trial, when it is conducted, and the medical practices of the investigators and clinics involved (CPMP 1995). Multicenter trials help to reduce the influence of such factors; however, if a multicenter trial is not feasible, every effort should be made to reduce the variations that can be caused by these factors.

Determining the sample size is another important component of clinical trial planning. Appropriate sample size depends on the design of the trial and its primary objective. Many methods and statistical models have been developed to calculate appropriate sample size. However, the number of participants in a clinical trial always should be large enough (but no larger than necessary) to provide a reliable answer to the questions posed.

The issue of sample size has been raised in the debate over placebo-controlled trials and equivalence trials. Most equivalence trials require more participants than placebo-controlled trials, an argument that has been used against them. Because placebo-controlled trials involve fewer subjects, they tend to be completed more quickly, and any resulting treatment is made available sooner (Levine 1998). The sooner a new treatment is introduced, the more people stand to benefit from its use. Others argue that in a well-designed trial and with the use of appropriate statistical methods, the required sample sizes for equivalence trials are often similar to those needed for placebo-controlled trials.[13]

Each of these issues in the choice of research design—equipoise, randomization, the nature and treatment of control groups, the distinction between efficacy and effectiveness studies, and the selection of the participant population and sample size—involves scientific questions that have ethical relevance (Freedman 1987; Levine 1986; Sutherland et al. 1994) and are therefore properly the concern of ethics review committees. One additional issue, which has been identified recently as important in the design of clinical trials and which has particular relevance to international collaborative research, is the involvement of the community and study participants in the design of research.

Involvement of the Community and Study Participants in the Design of Research

Over the past three decades, researchers increasingly have deliberately involved communities in the design of research (Arole and Arole 1994; CDC 1997; Taylor 1970; Taylor 1983; Taylor 1984). In addition, research participants, health advocates, and other members of the communities from which participants are recruited have requested, and in some cases demanded, involvement in the design of clinical trials. These trends are noteworthy. By consulting with the community, researchers often gain insight about whether the research question is relevant and responsive to the health needs of the community involved. In addition, community consultation can improve the informed consent process and resolve problems that arise during this process because of the use of difficult or unfamiliar concepts. Such discussions can provide insight into whether the balance of benefits and harms in the study is considered acceptable and whether the interventions and follow-up procedures are satisfactory. Community consultation also can reveal the best methods for recruiting participants. (See Chapter 3 for a more extensive discussion of community involvement in the recruitment of participants and the informed consent process.)

The Joint United Nations Programme on HIV/AIDS (UNAIDS), for example, has since its inception in the mid-1990s promoted the involvement of local communities and prospective research participants in the design and implementation of research studies. UNAIDS has an Ethical Review Committee—the duties of which include the basic IRB function of ethical review of research protocols—and this committee's standard assessment form includes a section entitled "Community Involvement and Impact." The following questions are included in this section:

- Is there a process of community consensus-building prior to initiating the research, i.e., consultation/discussion of impact of study and its relevance to (a) potential beneficiaries, (b) participants' communities? If not, why?[14]

  and

- To the degree possible, are (a) potential participants; (b) beneficiaries; (c) other community members; (d) local researchers, involved in: (i) the design; (ii) evaluation; (iii) analysis; (iv) publication and/or dissemination of the proposal; (v) implementation of results? If not, why?[15]

Researchers submitting proposals to UNAIDS receive a copy of the assessment form used by the Ethical Review Committee and are made aware of the need to address the issue of community involvement in the preparation of a research proposal for submission to UNAIDS.

In anticipation of the initiation of an increasing number of HIV/AIDS preventive vaccine trials, UNAIDS issued a guidance document in February 2000, in which Guidance Point 5 recommends the following:

> To ensure the ethical and scientific quality of proposed research, its relevance to the affected community, and its acceptance by the affected community, community representatives should be involved in an early and sustained manner in the design, development, implementation, and distribution of results of HIV vaccine research (UNAIDS 2000, 19).

However, it is frequently difficult to define the relevant community of participants, no matter where the research is conducted. In cases in which no traditional community structure exists, local organizations or nongovernmental organizations often can assist in representing the interests of participants in the research process. A research project might involve participants from widely scattered communities—sometimes in several nations—and it might be logistically difficult to reach representatives of every location from which participants are drawn. In addition, in some communities social hierarchies or corrupt elements exist that might impede the consideration of research participants' interests; therefore, in each research setting, it is necessary to determine the most appropriate way to involve local representatives who can provide a voice for research participants.

> ***Recommendation 2.3:*** **Researchers and sponsors should involve representatives of the community of potential participants throughout the design and implementation of research projects. Researchers should describe in their proposed**

protocol how this will be done, and ethics review committees should review the appropriateness of this process. When community representatives will not be involved, the protocol presented to the ethics committee should justify why such involvement is not possible or relevant.

Other Issues in Research Design

Although this chapter has focused primarily on the ethical issues that arise in the design of clinical trials, two additional issues warrant mention—monitoring the interim results of a study and repeating a study.

Monitoring the Interim Results of a Study

Randomized clinical trials begin at a point of equipoise regarding the relative risks and benefits of the intervention being evaluated. As the study proceeds, however, cumulative data or recent findings from other research efforts may provide strong evidence in favor of one of the interventions being tested, thus overturning the equipoise and suggesting that the study should be stopped. Responsibility for the review of interim data is often given to an independent group, such as a Data and Safety Monitoring Board (DSMB), with expertise in the clinical problem, biostatistics, and bioethics. DSMBs have confidential access to interim results, which are not available to investigators or sponsors. Unblinding investigators and sponsors would introduce bias into the trial and undermine its integrity. The goal of interim analysis is to stop the trial early if the superiority or inferiority of the experimental intervention being tested has been clearly established, if it is evident that the experimental intervention has no efficacy, or if unacceptable adverse effects are occurring (CPMP 1995; DeMets et al. 1999).

In addition to examining the evolving results of the trial, groups that are conducting interim analysis should be aware of advances in the field and assess whether study designs remain ethically and scientifically valid. This is especially important for studies that involve diseases for which rapid progress in the development of effective therapies has occurred. For example, trials in which the control group receives an established effective treatment may be deemed unethical because a new treatment has been found that is clearly more effective. In addition, trials may no longer be considered ethical because they have no reasonable hope of leading to an unequivocal result, or they have already demonstrated a statistically definitive and clinically significant difference between the control group and the experimental arm. Trials that are deemed to be unethical should be terminated to protect the research participants, even if continuation of the research would be of interest to the medical and scientific communities. Because clinical trials often require several years to complete, it is important to monitor them regularly to safeguard the best interests of the participants.

Repeating a Study

A different situation arises when a treatment has been shown to be effective in a developed country and researchers propose to repeat the study in a developing country. What could justify repeating a study using the same research design? Several who provided comments to NBAC remarked that generally, an accumulation of evidence from many studies is needed in order to establish a new intervention as efficacious and to warrant changes in health policy or medical practice. Whether several studies of the same intervention constitute repetition or whether conditions or protocols among studies are different enough that genuinely new evidence is being collected may not be known until all of the data are examined. Dispute frequently occurs, even in the United States, about whether differences in study populations—such as race, sex, stage of disease, presence of other conditions, or environmental conditions—constitute scientific differences that necessitate further empirical research because they might have a material effect on the effectiveness of an intervention.[16] In principle, if there is no scientific reason to question the effectiveness of the new treatment in the developing country population, it would be ethically problematic to repeat the study. However, in practice, as mentioned above, it may be difficult to determine when valid reasons to repeat a study exist. In some cases, because different biological, social, and environmental conditions are found in different developing countries, new interventions must be studied in those countries to determine their effectiveness in those settings. In other cases it may be reasonable to presume that treatments that are recognized to be effective

based on data from the United States or other developed countries do not need to be studied in every country in which they are used.

Another possible reason to repeat a study is that policymakers in many countries will not accept the results of trials conducted elsewhere.[17] This reluctance can stem from legal or regulatory considerations or from the existence of a policy that requires a determination of the adequacy of other countries' scientific, technical, or ethical review procedures. However, a reluctance to accept data from studies conducted in other countries also may represent a political stance on the part of a ministry of health or legislative body—that is, a refusal to recognize the relevance of research results from other countries because of national pride or political rivalries or an unwillingness to accept the results of studies that are not conducted by local authorities. Although these reasons cannot alone serve as ethical justifications for conducting a study that has already been successfully conducted, the urgent health needs of a host country may lead developed country sponsors to decide that it would be unethical *not* to carry out the necessary research if the established effective treatment could not otherwise be made available to the population.

Conclusions

This chapter has focused on a specific set of ethical issues related to choosing research designs for clinical trials. The discussion of some alternative designs is intended to demonstrate that no single design is appropriate for answering all research questions. In addition, the very act of choosing a research question has ethical implications. NBAC does not try to draw a conclusion about the precise circumstances under which, for example, the use of a placebo is acceptable in a particular clinical trial. Rather, this chapter has identified a set of ethically and scientifically relevant considerations that must be taken into account from the earliest stages of research design and of which potential investigators, ethics review committees, research participants, and research sponsors must be aware.

NBAC recognizes that some will disagree with the position that, in general, researchers and sponsors should make every effort to design clinical trials that provide control group members with an established effective treatment. In taking this position NBAC seeks to apply the same ethical standard to research conducted in developing countries that is applied in countries where established effective treatments are available to the general population. To do otherwise would leave the door open to conducting research in a developing country that could not be conducted in a wealthier country, while still allowing the benefits to flow to the wealthier country. If one accepts the fundamental premise articulated in Chapter 1—that research should be responsive to the health needs of the host country—then the logical next step should be choosing an appropriate research design, one that does not exploit the populations of countries with few resources while permitting those countries to be the sites of research that could benefit their populations.

Notes

1 NBAC made recommendations in this area in two previous reports (NBAC 1998; NBAC 1999) that are just as relevant to the current discussion.

2 See Kass, N., and A. Hyder, "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations," 49–50. This background paper was prepared for NBAC and is available in Volume II of this report.

3 Goodman, S., Public comment submitted to NBAC. November 13, 2000.

4 Dickersin, K., Testimony before NBAC. December 2, 1999. Baltimore, Maryland.

5 Temple, R., Testimony before NBAC. September 18, 1997. Bethesda, Maryland. Meeting transcript, 7–8.

6 AMA, Public comment submitted to NBAC. Received November 15, 2000; FDA, Public comment submitted to NBAC. Received November 9, 2000; Temple, R., Public comment submitted to NBAC. Received November 13, 2000.

7 Temple, R., Public comment submitted to NBAC. Received November 13, 2000.

8 Temple, R., Testimony before NBAC. September 18, 1997. Bethesda, Maryland.

9 See Kass and Hyder, 53.

10 Sommer, A., Testimony before NBAC. September 16, 1999. Arlington, Virginia. Meeting transcript, 189.

11 See Kass and Hyder, 53.

12 Goodman, S., Public comment submitted to NBAC. November 13, 2000.

13 Lurie, P., and S.M. Wolfe, Testimony before the Committee on Government Reform and Oversight. U.S. House of Representatives. April 22, 1998. Washington, D.C. Available at www.house.gov/reform/hearings/healthcare/fda498/index.htm. Last accessed January 9, 2001.

14 UNAIDS, Ethical Review Committee. Assessment Form for Committee Review. Question 9.

15 Ibid., Question 10.

16 Bennish, M., Public comment submitted to NBAC. Received November 12, 2000; Goodman, S., Public comment submitted to NBAC. Received November 13, 2000.

17 Sommer, A., Testimony before NBAC. September 16, 1999. Arlington, Virginia. Meeting transcript, 179–180, 188–189, 215–218.

References

American Medical Association (AMA). 1999. "Current Opinions of the Council on Ethical and Judicial Affairs. The Use of Placebo Controls in Clinical Trials." In *American Medical Association Code of Ethics*, Part E-2.075. Chicago: AMA.

Arole, M., and R. Arole. 1994. *Jamkhed: A Comprehensive Rural Health Project*. London and Basingstoke: MacMillan Education Limited.

Barinaga, M. 1988. "Placebos Prompt New Protocols for AIDS Drug Tests." *Nature* 335(6190):485.

Benatar, S.R., and P.A. Singer. 2000. "A New Look at International Research Ethics." *British Medical Journal* 321(7264):824–826.

Centers for Disease Control and Prevention (CDC). 1997. *Principles of Community Engagement*. Atlanta, GA: CDC.

CPMP Working Party on Efficacy of Medicinal Products (CPMP). 1995. "Biostatistical Methodology in Clinical Trials in Applications for Marketing Authorizations for Medicinal Products." Note for Guidance III/3630/92-EN. *Statistics in Medicine* 14:1659–1682.

DeMets, D.L., S.J. Pocock, and D.G. Julian. 1999. "The Agonising Negative Trend in Monitoring of Clinical Trials." *The Lancet* 354 (9194):1983–1988.

Enserink, M. 2000. "Helsinki's New Clinical Rules: Fewer Placebos, More Disclosure." *Science* 290(5491):418–419.

Flaherty, M., and J. Stephens. 2001. "Pennsylvania Firm Asks FDA to Back Experiment Forbidden in U.S." *Washington Post* 23 February, A-3.

Fletcher, R.H., S.W. Fletcher, and E.H. Wagner. 1982. *Clinical Epidemiology: The Essentials*. Baltimore, MD: Williams and Wilkins.

Food and Drug Administration (FDA). 1999. "International Conference on Harmonisation; E10 Choice of Control Group in Clinical Trials: Draft Guidance." *Federal Register* 64(185):51767–51780.

Freedman, B. 1987. "Equipoise and the Ethics of Clinical Research." *New England Journal of Medicine* 317(3):141–145.

Freedman, B., C. Weijer, and K.C. Glass. 1996. "Placebo Orthodoxy in Clinical Research I: Empirical and Methodological Myths." *Journal of Law, Medicine, and Ethics* 24:243–251.

Hauck, W.W., and S. Anderson. 1999. "Some Issues in the Design and Analysis of Equivalence Trials." *Drug Information Journal* 33:109–118.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 1996. *ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice*. Geneva: ICH Secretariat, International Federation for Pharmaceutical Manufacturers Association.

Joint United Nations Programme on HIV/AIDS (UNAIDS). 2000. *Ethical Considerations in HIV Preventive Vaccine Research: UNAIDS Guidance Document.* Geneva: UNAIDS.

Levine, C. 1998. "Placebos and HIV: Lessons Learned." *Hastings Center Report* 28(6):43–48.

Levine, R.J. 1986. *Ethics and Regulation of Clinical Research*, 2d ed. Baltimore, MD: Urban and Schwarzenberg.

———.1999. "The Need to Revise the Declaration of Helsinki." *New England Journal of Medicine* 341(7):531–534.

Lilford, R.J., and J. Jackson. 1995. "Equipoise and the Ethics of Randomization." *Journal of the Royal Society of Medicine* 88(10):552–559.

Lind, J. 1753. *A Treatise of Scurvy in Three Parts. Containing an Inquiry into the Nature, Causes and Cure of That Disease, Together with a Critical and Chronological View of What Has Been Published on the Subject*. London: A. Millar.

Lurie, P., and S. Wolfe, Public Citizen's Health Research Group, and M. Klaus, University of California-San Francisco. 2001. Letter to Tommy Thompson, Secretary of Health and Human Services. February 22. Available at www.citizen.org/hrg/publications/1558.htm. Last accessed February 23, 2001.

Mann, B. 1999. "The Life Cycle of a Drug." *Rule Maker Portfolio*. October 25. Available at www.fool.com/portfolios/rule-maker/1999/rulemaker991025.htm. Last accessed January 9, 2001.

Meinert, C.L., and S. Tonascia. 1986. *Clinical Trials: Design, Conduct and Analysis*. Oxford: Oxford University Press.

National Bioethics Advisory Commission (NBAC). 1998. *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity*. 2 vols. Rockville, MD: U.S. Government Printing Office.

———. 1999. *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*. 2 vols. Rockville, MD: U.S. Government Printing Office.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission). 1979. *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Washington, D.C.: Department of Health, Education, and Welfare.

Office for Protection from Research Risks (OPRR). 1993. *Protecting Human Research Subjects: Institutional Review Board Guidebook*. Bethesda, MD: U.S. Government Printing Office.

Perinatal HIV Intervention Research in Developing Countries Workshop Participants. 1999. "Science, Ethics, and the Future of Research into Maternal Infant Transmission of HIV-1." *The Lancet* 353:832–835.

Pharmaceutical Research and Manufacturers of America (PhRMA). 1999. *1999 Pharmaceutical Industry Profile*. Washington, D.C.: PhRMA.

Rothman, K.J., and K.B. Michels. 1994. "Sounding Board: The Continuing Unethical Use of Placebo Controls." *The New England Journal of Medicine* 331(6):394–398.

Sackett, D.L. 1983. "On Some Prerequisites for a Successful Clinical Trial." In *Clinical Trials: Issues and Approaches*, eds. S.H. Shapiro and T.A. Louis, 65–79. New York: Marcel Dekker.

Spilker, B. 1991. *Guide to Clinical Trials*. New York: Raven Press.

Sutherland, H.J., E.M. Meslin, and J.E. Till. 1994. "What's Missing from Current Clinical Trial Guidelines? A Framework for Integrating Ethics, Science and Community Context." *Journal of Clinical Ethics* 5(4):297–303.

Taylor, C.E. 1970. "Public Health Research." In *Medical Research: Priorities and Responsibilities*. Proceedings of a Round Table Conference Organized by the Council for International Organizations of Medical Sciences (CIOMS). Geneva: CIOMS.

———. 1983. "Health Systems Research: How Can It Be Used?" *World Health Forum* 4:328–335.

———. 1984. *The Uses of Health Systems Research*. Public Health Paper No. 78. Geneva: World Health Organization.

Temple, R. 1996. "Problems in Interpreting Active Control Equivalence Trials." *Accountability in Research* 4:267–275.

World Medical Association (WMA). *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* (adopted 18th WMA General Assembly, Helsinki, Finland, June 1964; amended: 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; and 52nd WMA General Assembly, Edinburgh, Scotland, October 2000). Ferney-Voltaire, France: WMA. Available at www.wma.net/e/policy/17-c_e.html. Last accessed January 12, 2001.