Primum Non Nocere:[1] Implications for the Globalization of Biomedical Research Trials

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International medical trials performed on subjects of one country by multinational corporations are becoming more commonplace as globalization extends into more areas of human and commercial activity. Governments and corporations use these experiments on humans to test new therapies. Clearly, these human experiments are essential for advancing the state of knowledge in biomedicine. They serve as the cornerstone for fundamental developments in understanding how the human body functions in the normal and disease states, and how specific therapies affect people with illnesses. Dr. Norman Howard, a key international bioethicist, remarked that, "Human experimentation is the *sine qua non* of medical progress." For biomedical science to be a continuing success, important ethical concerns will have to be balanced with the scientific and commercial payoffs that these experiments promise to provide. Another essential part of the solution to issues of ethics in trials must be the continued internationalization of ethical and scientific intercourse standards in the setting of human experimentation. This global ethical and scientific intercourse is critical to the maintenance of physician trust, the future recruitment of experiment subjects, and the protection of internationally recognized human rights.

Multiple factors come into play in biomedical research projects involving human subjects. In most situations, these factors can be organized into three groups of conflicting concerns. The first of these groups is comprised of scientists and biomedical researchers who are primarily concerned with the experiment's statistical framework and the demonstration of a significant difference between therapies or outcomes. They are also interested in showing that a therapy works consistently and safely in a scientifically predictable manner. Second, there are commercial representatives who are often interested in minimizing the costs of

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pharmaceutical development and state drug agency licensing protocols, and delivering a drug to the markets as quickly as possible. The third group is made up of the ethicists who look at a study's methods to determine if the principles of biomedical ethics are upheld and if its implementation is just. They are primarily concerned with the rights of research subjects and the obligations of researchers to the subjects.

This article highlights several areas of concern present in discussions of international research trials on humans. Concerns of ethicists will be portrayed along with the concerns of scientists and international business people. The article will also introduce key issues that need to be addressed as governments and commercial entities conduct more international trials. Finally, potential solutions to the ethical dilemmas of international trials will be suggested. The ideas of increasing standardized national and international monitoring, developing punitive mechanisms for ethical infractions in trials, and maintaining market mechanisms and commercial incentives for drug development will be explored. Future developments can both bolster the international human rights framework as it pertains to human experimentation and generate fruitful mechanisms for states and businesses to involve international populations in research endeavors for the benefit of patients worldwide.

THE CLINICAL TRIAL: A HUMAN EXPERIMENT

The primary goal of a clinical trial is to demonstrate a significant difference between treatments. Physicians can then use this information to treat their patients with the proven, superior method. For the trial to be ethical, it should be conducted only when the current clinical evidence for the alternative treatments is balanced or ambiguous, leaving the physician uncertain as to which treatment is superior. The U.S. Food and Drug Administration's (FDA) clinical trial regulations describe the purpose of a clinical trial as distinguishing "the effect of a drug from other influences, such as spontaneous change in the course of a disease, placebo effect, or biased observation. Reports of adequate and well controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs..."[2]

The design of a clinical trial is essential in determining the types of conclusions that the trial can demonstrate, the number of participants required, the duration, and the power that the study design has in demonstrating the effects of various treatments and in minimizing trial errors. Although there are many trial designs, the current gold standard clinical trial used to produce substantial evidence for effectiveness is a double blind randomized placebo-controlled clinical trial. This trial design relies on dual randomization and blinding of the population of treatment providers and subjects so that neither knows who has the new treatment and who has the placebo control. The randomization of participants and providers, as well as their lack of knowledge regarding which treatment they are providing or receiving, reduces trial bias and improves trial power. Using a placebo control tends to reduce the number of participants required and can often result in improved trial power in demonstrating significant differences between treatments.[3]

For a trial to be ethically designed, the human experiment must cease at the point when clinical equipoise is disturbed. Clinical equipoise must exist at all points along the experiment trajectory. In other words, the trial must be discontinued when the researchers demonstrate a treatment preference. Scientific review of trials and endpoints is largely a process of peer review in Europe and the United States. An ethical review board or an institutional review board (IRB) is composed of a diverse group of individuals and is responsible for ascertaining a trial's compliance with ethical standards and must validate the ethical components of a trial.

INTERNATIONAL AGREEMENTS FOR RESEARCH ON HUMANS

Although many physicians have historically been concerned with the ethical status of clinical trials, the ethical notions of clinical research have only been rigorously discussed and codified in the last century. In the twentieth century, the history of human experimentation in biomedical research has been dramatically linked to torture and cruel and inhuman punishment, most noticeably in Germany during World War II. The Nuremberg Code, developed in 1947, provided a mechanism for judging physicians who had conducted medical experiments on prisoners of German concentration camps. The Code stipulated that, in the case of research on humans, "voluntary consent of the human subject is absolutely essential."[4] This requirement was designed to remove coercion, ignorance, and involution from the subject's decision to enter the study. The Declaration of Helsinki, issued by the World Medical Association in 1964, included a similar requirement for informed consent and became a second key document detailing the standards for human experimentation. The Declaration also provided that "every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method..."[5] In 1966, the U.N. General Assembly adopted the International Covenant on Civil and Political Rights, which reaffirmed the importance of requiring voluntary informed consent. Specifically, Article 7 mandates that, "No one shall be subjected to torture or to cruel, inhuman, or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation."[6] The language of the Covenant speaks to the importance of the issue of human medical experimentation as it links bioethics and international human rights law.

In 1982, the Council of the International Organization for Medical Sciences (CIOMS) and the World Health Organization (WHO) developed the Proposed International Guidelines for Biomedical Research Involving Human Subjects. This document detailed the manner in which the ethical principles outlined by CIOMS and others could be effectively and pragmatically applied. After years of review, this proposal was accepted as the International Guidelines in 1992 by the CIOMS. This implementation document has three general themes. The first focuses on individual consent and community agreement for participation. It is primarily concerned with the education of prospective subjects regarding voluntary participation, and study design and expectations. The second implementation theme reinforces the importance of bioethics review mechanisms by proposing the establishment of national and local committees to study and develop review mechanisms. The final theme details the sponsor obligations and requirements. These include providing medical service access, compensation, and care for injuries resulting from research, technology transfer, and research and development processes to institutions in host countries.

A later document of this set concerned with the protection of human subjects, the International Harmonization Guidelines of the CIOMS, asserts that all research involving human subjects should be conducted in observance of these three ethical principles.[7] This 1993 document also mandates that the ethical standards of the country of the sponsoring organization should be used to determine guidelines in international trials. After review in the sponsoring country, the local ethical review mechanisms of the host state must also be satisfied. More recently, national efforts have begun to address international research concerns. In the United States, the National Bioethics Advisory Commission has recently drafted a document entitled "Ethical and Policy Issues in International Research," which represents a balanced view of many of the international developments in bioethics. Additionally, a thorough review of the compendium of developed and developing international guidelines in bioethics has been assembled by Sev S. Fluss of the WHO Office of Health Policy in Development.[8] The implementation of these policies in the last 50 years has significantly slowed, but not extinguished, the presence of abuse.

PHILOSOPHIC PRINCIPLES AND NEW ISSUES

The documents described above highlight four central ethical principles that frame the ethical responsibilities of clinical trial sponsors. Each principle will be briefly discussed in light of several issues that arise in the context of international trials.

The Principle of Respect for Persons. For ethicists, the principle of respect for persons is intimately linked with the philosophic provision of respect for autonomy that must be afforded to all research participants.[9] Autonomy refers to the notion that each person is able to voluntarily define his course of action through an internally determined set of plans and goals unaltered by coercive influences. The voluntary decision to grant consent is considered an informed decision if "consent [is] given by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation."[10]

Regulatory systems differ in their implementation and oversight of the informed consent requirement. Some require extensive paperwork while others require admission by a clinician alone. The United States regulates informed consent by requiring that consent be obtained in most situations, preferably in writing, after the prospective participant has been properly educated and given an adequate opportunity to consider benefits, risks, alternatives, and the trial protocol in an environment that minimizes coercive forces or undue influence.[11]

New Issues in Informed Consent. In some cultures, community leaders can have a direct and powerful effect on individual decision-making. One author states that, "In many African countries, there is no concept of the individual beyond one's role in the community. Who will consent for subjects in such a culture?"[12] Consent may require obtaining permission from a community leader before approaching individuals. Dr. Robert Levine, a prominent international bioethicist, has further pointed out that the concept of 'person' is so different in Western and non-Western societies that it significantly influences the issue of informed consent.[13]

Coercive influences also arise in the context of international research on humans. Since delivery of health care in developing countries tends to be considerably inferior to that in developed countries, citizens of developing countries may enter trials solely to gain access to otherwise unobtainable healthcare for their community or themselves. Truly informed consent can only be achieved by undertaking an unbiased assessment of the influences that are involved in a prospective subject's interest in joining a trial and by including community leaders as partners at every step. Additionally, local cultural influences should be an integral part of determining how these principles are implemented in a trial.

The Principles of Beneficence and Nonmaleficence. Medical ethicists often relate the principle of beneficence to the Oath of Hippocrates that reads in part, "I will apply dietetic measures for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice." The first sentence obliges physicians to employ beneficence, or, to be concerned with promoting the good of their patients. The second sentence resonates with the idea that physicians must be concerned with preventing maleficence, or injury and harm to their patients in the course of delivering medical treatment. These principles can often be difficult for clinicians to apply in clinical research, as the goal is primarily to advance the state of knowledge, not the present state of health of the individual patient. Balancing the degree of risk to the subject with the importance of the knowledge gleaned from the study then becomes the ultimate ethical concern of research review bodies. The Nuremberg Code describes this balance, stating, "The degree of risk to be taken [by the subject] should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment."[14] Thus one is forced to weigh the benefits and risks to society against the benefits to the individual.

New Issues for Placebos and Trial Risks. The use of the placebo in the design of clinical trials has been a mainstay of biomedical research for decades. This has resulted in recent controversy, however, as more trials are conducted internationally under varying healthcare and judicial systems. The FDA and other drug regulatory bodies often require the use of a placebo control arm in trials so that a demonstration of efficacy can be firmly established.[15] Many scientists also believe that the placebo must be used "if the true efficacy of an active treatment is to be measured."[16] Further, it has been argued that a problem raised with active controls involves the inability to decide on a gold-standard comparator.[17] There is currently no generally accepted maxim regarding the specific use of placebo in the international setting where the sponsor and host health care systems are dramatically different.

As enunciated in the Declaration of Helsinki, the patient that enters a clinical trial should be guaranteed to receive at least the current best-accepted treatment for the disease under study. Critics argue that the risk, or maleficence, of using a placebo control is too great when there is a better, standard treatment available. This raises an ethical question prompted by the use of the sponsor standard of care in host trials. Indeed, if at a trial's completion, the host cannot afford either the sponsor's standard treatment or the novel treatment, how ethical is the trial?

Many recent investigators have questioned the ethics of placebo use, especially in studies where the risk to subjects is high. This concern is raised regardless of possible trial benefits to local populations that cannot afford the standard treatment. However, this may be a concern that pertains only to certain situations. If the sponsors are to be held accountable to the standard of care in their country, how can they conduct the study of a novel, significantly less expensive treatment (where expensive refers largely to production and distribution and not to marketing costs) with less efficacy than the currently acceptable sponsor standard, which may have great applicability to the developing population of the host state? Even though the concept of beneficence could be applied universally, regardless of state borders or economic conditions, it may not reasonably follow that the definition of beneficence requires that states which cannot afford treatments available elsewhere should be denied research that may lead to treatments that are more cost effective for their populations. If the trial is intended to benefit the populations where the trial is conducted (and this has been agreed to before the trial commences), and if the trial is designed to use a placebo, the standard of care in that country, the trial may be considered ethical. In fact, it may be unethical to prevent the trial from occurring solely for the reason that people in developing countries, on average, are unable to afford the expensive and perhaps superior technology that more developed countries possess.

As an example of this dilemma, in April 1997, the U.S. ethics watch dog organization Public Citizen criticized the use of a placebo control in U.S.-sponsored trials of the anti-HIV drug AZT in Africa to prevent the mother-to-child transmission of HIV in an HIV infected mother. Public Citizen argued that since AZT had already been proven to reduce transmission, a placebo trial in Africa was unethical, even if the discovery of a more cost effective and relatively equal therapeutic regimen was the trial's goal. Peter Lurie and Sidney Wolfe, advocates for Public Citizen,[18] also charged that the trial conducted in Africa was unethical because the use of a placebo in the trial would have been considered substandard of care in the United States, the sponsor country. "Protests from Africa, in particular, argued that the epidemiology of HIV on that continent and the reality of what was affordable there meant that a placebo control was still ethical."[19] This situation requires analysis of three points. First, if a trial is considered unethical in the country performing the trial, should it be administered by that country at all? Second, are trials conducted in host countries ethical if they are considered unethical in the administering country? Third, what should the standard be if the sponsor is a multinational firm?

The Principle of Justice. One result of applying the principle of justice to scientific research is the imperative that the populations that are involved as subjects of the research must be recipients of the benefits of that same research. Although an assessment or calculation of research benefits at both the individual and population level is often difficult to render, it is clear from the application of this principle that one population should not be used experimentally to serve the ends of another population.

New Issues for Justice in Clinical Trials. The analysis of justice in international trials raises a number of concerns. A central concern involves the use of placebos. Again, if a country's economic situation prevents its citizens from gaining access to the standard treatment for the disease under investigation, is it ethical for a country capable of providing the medical standard treatment to test other treatment options in the host population?[20] Fundamentally, it is only just to enlist subjects in a host country if the study's results will be used to better the treatment of patients in that population. An additional issue needs to be discussed in light of these economic concerns. Presumably, the drug is too expensive to the host population because of the price set by the multinational corporation producing the drug, and not because of host state-controlled import tariffs or manufacturing costs. Justice, as described above, requires that trial sponsors make efforts to make the drug reasonably available to the population enlisted under the study. Agreements between host populations and trial sponsors should be required before trials begin. One assessment of whether a trial is just would be to compare sponsor obligations, agreed to at the outset, to a predetermined scale. A three-tiered scale including a minimum standard, a substantial standard, and an ultimate standard, is a way of measuring sponsor compliance in the event that a successful drug is produced:

> *Minimum standard of justice:*
> The drug is made available to the testing population at a price determined by the multinational.[21]
>
> *Substantial standard of justice:*
> The drug is delivered to the test country at a price at or between the cost offsetting any savings realized by performing the tests in the host country rather than in the other countries where the drug is sold, or at a price involving only manufacturing, distribution, and overhead costs (excluding marketing costs).
>
> *Ultimate standard of justice:*
> The drug is made available at a price that allows a majority to all of the afflicted people in the host country to have access to it.

In this framework, a failure to make a drug available at any price would be a failure to meet the minimum standard of justice, and would certainly make the trial unethical.[22] Sponsors and local leaders should collectively decide what tier of justice would be acceptable to both parties before the trial's commencement, thus helping to ensure that the trial is an ethical one.

Several alternatives exist, however, which might benefit host populations more than just merely making the drug under study reasonably available or even free, using the simple framework above. For example, it may be in the best interests of both the multinational corporation and the host state to negotiate an agreement under which several drugs are supplied to the host country so that the total health benefit to the host population is at least equivalent to, and possibly greater than, making reasonably available only the single drug under study. If this multiple drug solution is to be considered just, which is debatable, the measurement of aggregate health benefit would be an important component of the balancing process. This is not to say, however, that some of the benefits of the research are not extended to a host population afflicted with the disease under examination. The aggregate health benefit would require a minimal to substantial standard of justice for populations with the disease under study and additional health benefits for other patient populations who might be helped by the corporation's suite of other drugs.

PROPOSALS FOR IMPROVING THE APPLICATION OF ETHICS

Frederick T. Gates, an influential force in the creation of the Rockefeller medical philanthropic empire, remarked decades ago that "the values of medical research are the most universal values on earth and they are the most intimate and important values to every human being that lives."[23] Today we are in a unique era in the history of medicine, where the rapid rate of drug discovery is dramatically changing the face of human suffering. This new era requires both vigilance in maintaining the highest ethical standards in human research, and proper and effective implementation of these standards without impeding the developments of pharmaceutical research, in both the commercial and noncommercial realms.

I. DEVELOPING MONITORING MECHANISMS

The IRB and its relatives across the globe are designed to provide ethical and, in some locales, scientific oversight to research trials. Many advances have been made to ensure that IRBs are unbiased, disciplined, and composed of a variety of individuals that can effectively address research concerns. These elements are important as research extends beyond national borders, and as corporate interests mix with scientific and ethical interests.

All too often, IRB participants remark that inadequate support is given to their task, a fact that, if true, can hurt the effectiveness of the committee. In the developing world, where adequate healthcare is often unavailable, the notion of expending resources to ethically review research can be frustrating for host country trial administrators. Even in the United States, excessive workloads and inadequate resources of IRBs have been reported to result in less-disciplined and often insufficient trial supervision.[24] Add to this the requirement that IRBs in developing countries must finance the approval and possible re-approval process of trial implementation in order to comply with sponsor governments. Thus, some of the international IRB review activities are almost doomed from the start.[25] The onus, then, must fall on international organizations and sponsors to provide funding and access to impartial educational services in order to ensure that ethical review mechanisms are in place in the host country. A necessary precondition for adequate ethical review, then, might be adding IRB funding requirements to any research proposal or effort involving human subjects. IRB funding should be considered a relevant adjunct to the scientific funding required for a trial.

Independent prospective review in both countries and protocols that conform to the laws of the host country should serve as the de facto oversight standard. This point is stated in the CIOMS Guidelines: "Committees competent to review...aspects of clinical trials must be multidisciplinary...In many cases such committees operate most effectively at the national level."[26] Thus, a national committee, or a nationally licensed committee, composed of exemplary members of IRBs could be used in situations involving multinational or international efforts to ensure adequate and disciplined project review. As one example, British government guidelines for Institutional Review Boards require that the District Health Authority appoint the chair and vice-chair. Further, monitoring studies should be prioritized based on certain characteristics. These characteristics, in order of greatest to least importance, include: the level of risk to trial participants; the level of education, information and consent that is implemented; and the proposed solution to the problem of justice for the testing population involved and other populations in the host state.

Cultural, economic, technological, and other differences among global populations also make the task of setting guidelines for the implementation of ethical principles a difficult one. Ethical principles should be immutable, yet their guidelines should be flexible in order to allow for changes in both implementation and culture. The influence of tribal leaders in West Africa, for example, has significantly diminished over the past decades, possibly requiring a change in the manner in which ethical principles are implemented in studies there.[27] An informed consent mechanism that was designed to take into account the influence of tribal leaders is now largely out of date, but the importance of the principle of autonomy is still valid. Therefore, principles that have been generally agreed upon internationally should be preserved across cultures, but their specific implementation details might be left to the joint efforts of local authorities and international sponsors.[28] However, universal principles must also be maintained. Dr. Marcia Angell, previous Editor-in-Chief of the *New England Journal of Medicine* remarked succinctly that, "There must be a core of human rights that we would wish to see honored universally, despite local variations in their superficial aspects...The force of local custom...cannot justify abuses of certain fundamental rights..."[29] Thus, composite review by both the host and sponsors should be required, but local custom should be used in dictating the manner in which principles are implemented.

2. MAINTAINING BENEFITS FOR COMMERCIAL DRUG DEVELOPMENT

Multinational pharmaceutical firms are primarily interested in staying in business through the effective management of their product portfolios. These businesses are very concerned with innovation, as their success hinges on the efficient development of therapeutic devices that can be sold for a profit worldwide.[30] Corporations, with their scientists and employees, act as innovators, clinical trial investors, distributors, and profit generators. Therefore, maintaining commercial incentives and patent protections for drug development while ensuring ethical stringency becomes essential in discussions of innovation and the future benefits that medical science can provide. This requires international cooperation to protect the intellectual property rights of people and organizations involved in drug development. Ethical action may come, in some circumstances, at the expense of innovation or drug development.

Since a single country's laws only apply within its borders, multinational enterprises can decide which environment best suits their development needs as well as determine prices for the drugs on a local basis. These are advantages produced by globalization. However, the process of globalization may also bring increased international regulatory requirements that are likely to have an adverse effect on innovation and development as well as drug pricing and distribution. Additional factors of the analysis are necessary before regulatory policies are expanded or patent protections are reduced since both may significantly interfere with innovation or pharmaceutical development and distribution.[31]

Ethical concerns are necessarily tied to practical discussions of justice in health care delivery and drug development. Drug development is a large economic enterprise. Estimates show that the regulatory requirements of the United States, coupled with research and development costs, make the total cost of developing a new drug between $100 and $500 million. This alone limits the types of diseases that companies target for research. To disregard economic concerns for ethical standards is to overlook the massive economic force required to bring these new treatments to market. As stated, there may be minimum, substantial, and ultimate standards of justice, but each has a cost that may constrain the number of new therapeutics developed. A goal for the implementation of philosophic principles is to ensure that they are strictly adhered to in the most translucent way possible.

There are several important factors to take into account when considering the ethics of international drug trials. First, new drugs are only made available as a result of innovation. Second, drugs are made available to patients via regulatory and distribution channels. Third, drugs must be affordable for patients. Innovation requires educational and patent protection mechanisms that enable institutions to produce and protect new pharmaceutical ideas. Regulatory and distribution channels represent vital elements of a developed marketplace. Rising pharmaceutical costs and the healthy profit margins of international pharmaceutical companies have led to discussions of price fixing, the reduced length of patent schemes, and other market interruptions. There is not an accepted assessment of the manner in which innovation, possibly measured as the number of novel drugs released per decade, is affected by the compendium of various regulatory schemes, licensing hurdles, or trial protocol requirements.

Many argue that these corporations act to boost their profits, which is clearly true. However, multinational drug companies are responsible, at least in part, for the development of as much as 90 percent of all new pharmaceuticals, according to some industry representatives.[32] Although one cannot overlook the integral importance of academia and government funded research in drug innovation, corporations do much to advance these technologies from the innovation stage to the development stage for the production of useable, widely available, and distributable drugs.

Corporate concerns must be considered in an integrative manner when developing international trial and drug licensing policies, enforcement mechanisms, and monitoring frameworks. Policymakers must be careful to avoid significantly hindering pharmaceutical innovation through market tampering. We face an economic and ethical dilemma that requires us to effectively balance concerns to keep studies ethical while prizing innovation in the market. The balancing act is a sensitive one. On the ethical front, we must be careful to ensure the global well being of patients involved in clinical research. On the economic front, we should maintain competitive market mechanisms and intellectual property protection that reward and invite rapid pharmaceutical innovation.

3. CREATING ENFORCEMENT MECHANISM AND PENALTIES

The vast majority of research on humans conducted today is performed in an ethically sound manner with the highest interest in keeping subjects from harm. However, ethical infractions of any kind erode patient and public trust in biomedical research. In the words of Donna Shalala, former Secretary of U.S. Health and Human Services, "If we cannot guarantee sound research...and patients' safety...public support will evaporate."[33]

Over the past 50 years, the international community has agreed to principles that now frame the conduct of research on humans. The rights of society, science, or future persons afflicted with disease must be considered a secondary concern, with primary respect given to the rights of trial subjects. However, these principles are not backed by enforcement measures. Surveillance and reporting on clinical trials by governmental and nongovernmental organizations are moves in the right direction, but a more potent and disciplined mechanism of enforcement in the case of infractions should be developed.

One step is to advance the relationship between international human rights law and the international bioethics documents.[34] Some of the principles in the international bioethics documents cited above are linked to human rights conventions and the defined standards of accepted international human rights law.[35] This is certainly a start, although juridical powers may be ill suited for the handling of most of the disputes. State and international mechanisms must also be developed. This will require additional standards of international law and a more substantive collection of relevant court rulings. Although state enforcement would still be necessary, international cooperation in this area is likely to prove crucial.[36]

Another solution is for states to develop sanctioning or other punitive mechanisms for infractions. The existence of sanctions may act as a deterrent against unethical actions. This punishment philosophy is adequately addressed in current CIOMS documents.[37] Before leaving office, Shalala proposed that the U.S. FDA be allowed to "levy civil monetary penalties for violations of informed consent and other important research practices...Financial penalties and administration actions will give the agency a wider range of tools for disciplining researchers, sponsors, and institutions that do not follow guidelines."[38]

Additionally, state monitoring boards could require registration of all international experiments and insist that research administrators demonstrate adherence to the three central ethical principles of biomedical study before and during the trial, and at the time of gaining approval for pharmaceutical distribution. However, state government safety and licensing authorities should not be heavy-handed. Rather, they should ensure that adequate measures are taken to maintain agreed-upon tenets of research and more specifically the application of justice. Dr. Eran Bellin, a U.S. physician, in a letter to the *New England Journal of Medicine,* offered a tentative version of this solution: "First, require all trials undertaken by pharmaceutical companies to be registered with the FDA, with end points specified in advance. Failure to register studies in advance would make their results inadmissible as evidence in FDA studies of efficacy."[39] This measure might safeguard subjects involved in both government and commercial trials. In short, state measures of enforcement may provide impetus to both governmental and nongovernmental entities to ensure that projects closely adhere to ethical principles. Again, however, regulations should be used in the most transparent way possible to protect trial subjects, without unnecessarily impeding or slowing innovation and development.

CONCLUSIONS

We are living in an exciting time in medical science development. Medical science is transforming the way in which people live, their quality of life, and their expectations. Development means change and requires new thinking on the manner in which research on humans is performed. The overarching goal is to advance the human condition in a way that is just and reasonable. In international research, subjects need to be protected, scientists need to be able to pursue their lifesaving work, and corporations need to be allowed to innovate and develop pharmaceuticals in a reasonably free market.

As argued, the engine of pharmacological innovation must be a secondary concern; the patient subject must be the ultimate one. Success will be measured not only by what innovations scientists develop, but also by the manner in which those innovations are developed and the number of people they reach. To achieve this version of success, the combined efforts of physicians, scientific researchers, commercial interests, international lawyers, and ethicists will be necessary to ensure that the proper standards of economy, science, and ethics are followed.

Although there are several possible leaders of this effort, the WHO and national health authorities can and should serve the unique purpose of developing an extended research system, in which international mechanisms for scientific and ethical review of ongoing studies could be coupled with efforts to create punitive mechanisms that enhance compliance while maintaining a healthy international environment for corporate and government pharmaceutical research. Additionally, governments must be committed to using public funds to provide reasonable health care standards, which includes public payment of pharmaceutical treatments for their citizens.

Although new developments may be sought to enhance international efforts to guide clinical trials and their development, the idea that the promotion of health extends into many areas of society, including commerce and law, is not new. The idea of inclusion of societal aspects in the effort of health promotion was clearly emphasized in the World Health Declaration of Alma-Ata in 1978, where health was described as a "social goal whose realization requires the action of many other social and economic sectors in addition to the health sector."[40] If properly managed, continued achievements of this social goal of health promotion in the new world of globalization of clinical trials will prove, through new drugs and enhanced access, to be both a benefit and achievement for all. ■

NOTES

1 "First, Do No Harm."

2 U.S. Food and Drug Administration, 21CFR 314.126, "Adequate and Well-Controlled Studies," 1985.

3 M.R. Tramer, D.J.M. Reynolds, et al., "When Placebo Controlled Trials are Essential and Equivalence Trials are Inadequate," *British Medical Journal* 317(7163) (September 26, 1998): 875-880.

4 The Nuremberg Code, 1947.

5 World Medical Association Declaration of Helsinki, Article II.3, 1964, 1975, 1983, 1989 (Hong Kong).

6 International Covenant on Civil and Political Rights, 1966.

7 "CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects," 1993.

8 S.S. Fluss, "International Guidelines on Bioethics," Supplement to the *EFGCP News* (December 1999).

9 Guideline 1 of the Council for International Organizations of Medical Sciences (CIOMS), "International Ethical Guidelines for Biomedical Research Involving Human Subjects."

10 Ibid; and Department of Health and Human Services, "Regulations for the Protection of Human Subjects," 45 CFR 46, 46.116, "General Requirements for Informed Consent."

11 Department of Health and Human Services, "Regulations for the Protection of Human Subjects," 45 CFR 46.

12 "Trials of HIV Vaccine Planned for Developing Countries," *British Medical Journal* 303 (1991): 1219-1220.

13 R.J. Levine, "Informed Consent: Some Challenges to the Universal Validity of the Western Model," in Z. Bankowski, J.H. Bryant, and J.M. Last, Ethics and Epidemiology: International Guidelines (Geneva: CIOMS, 1991), 47-58.

14 The Nuremberg Code, 1947.

15 Although the FDA has added advisories to its policies that ask for data demonstrating effectiveness relative to control groups that may allow the usage of active controls (drugs that are known to be active), the original text of the FDA study guidelines demonstrates the commitment to the gold-standard placebo study. Food and Drug Administration 21 CFR 314.126, "Adequate and Well Controlled Studies," 1985.

16 L.E. Ramsay, "Commentary: Placebo Run Ins Have Some Value" *British Medical Journal* 314 (7088) (April 19, 1997): 1193.

17 Tramer, Reynolds, et al., 875-880.

18 P. Lurie and S.M. Wolfe, "Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries," *New England Journal of Medicine* 337 (1997):853-856.

19 Editorial, *The Lancet*, January 24, 1998, 225.

20 Proceedings of the XXVIth CIOMS Conference, Geneva 1992, Report of Working Group A: "Informed Consent." (Moderator: J.M. Last).

21 "CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects-1993," Guideline 8.

22 Minimal justice is illustrated using the example of the drug eflornithine, used in the treatment of African trypanosomiasis and developed in part with studies conducted in Africa. The drug was released in Africa at a prohibitively expensive (and hence locally 'available' but economically unavailable) price near $300 per treatment course. One situation demonstrating ultimate justice was the availability of ivermectin for the large-scale treatment of filariasis in Africa.

23 Brown, *Rockefeller Medicine Med*, 122.

24 "Institutional Review Boards: Their role in Reviewing Approved Research," Department of Health and Human Services, 1998.

25 Professors Abdussalam and Osuntokun, in speaking on issues of IRBs in the developing world, have eloquently made the point that developing countries often have insufficient resources for health care delivery or ethical review of research projects. See M. Abdussalam and B.O. Osuntokun, "Capacity Building for Ethical Consideration of Epidemiological Studies: Perspective of Developing Countries," in Z. Bankowski, J.H. Bryant, and J.M. Last, eds., *"Ethics and Epidemiology: International Guidelines,"* Proceedings of the XXVth CIOMS Conference (Geneva: CIOMS, 1991), 126-136.

26 "CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects-1993," Guideline 14.

27 O.O. Ajayi, "Taboos and Clinical Research in West Africa," *Journal of Medical Ethics* 6 (1980): 61-63.

28 This idea is preserved in the CIOMS Guidelines, which resolves that "the ability to judge the ethical acceptability of various aspects of a research proposal requires a thorough understanding of a community's customs and traditions. The ethical review committee must have as either members or consultants persons with such understanding." See "CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects-1993," Guideline 8.

29 M. Angell, "Ethical imperialism? Ethics in International Collaborative Clinical Research," *New England Journal of Medicine* 319 (1988): 1081-1083.

30 Remarks by Raymond V. Gilmartin, Chief Executives' Club of Boston, January 19, 2000.

31 C. Cornu, A. Cano, et al., "Could Institutional Clinical Trials Exist in Europe?" *The Lancet*, January 1999, 63-64.

32 "Why Do Prescription Drugs Cost So Much and Other Questions About Your Medicines," Pharmaceutical Research and Manufacturers of America, 2000.

33 Donna Shalala, "Sounding Board," *New England Journal of Medicine*, 343 (11) (September 14, 2000): 808.

34 United Nations Draft Convention for the Prevention and Suppression of Unlawful Experimentation.

35 International Covenant on Civil and Political Rights.

36 J.M. Mann, L. Gostin, S. Gruskin, et al., "Health and Human Rights," *Health and Human Rights* 1 (1): 7.

37 "CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects-1993," Guideline 14.

38 Donna Shalala, "Sounding Board," *New England Journal of Medicine* 343 (11) (September 14, 2000): 810.

39 Eran Bellin, "Letter to the Editor," *New England Journal of Medicine* 343 (7) (August 17, 2000): 511.

40 Declaration of Alma-Ata, "Health for All" Series 1, Geneva Health Organization, September 12, 1978.