The Pharmaceutical Industry's Responsibility for Protecting Human Subjects of Clinical Trials in Developing Nations

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Pharmaceutical companies increasingly perform clinical trials in developing nations. Governments of host nations see the trials as a way to provide otherwise unaffordable medical care, while trial sponsors are drawn to those countries by lower costs, the prevalence of diseases rare in developed nations, and large numbers of impoverished patients. Local governments, however, fail to police trials, and the FDA does not monitor trials in foreign countries, resulting in the routine violation of international standards for the protection of human subjects. This Note proposes independent accreditation of those institutions involved in clinical trials — the institutional review boards which oversee trial protocol; the organizations, such as pharmaceutical companies, which sponsor the trials; and the research organizations that conduct the trials. Accreditation, similar to that used in the footwear and apparel industries, would increase the transparency of pharmaceutical trials and would enable the United States government and consumers to hold trial sponsors accountable for their actions.

I. INTRODUCTION

In August 2001, thirty Nigerian families sued Pfizer, the world's largest pharmaceutical company, in the United States under the Alien Tort Claims Act, alleging that Pfizer had violated the law of nations in the course of clinical trials conducted during

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a meningitis epidemic in Kano, Nigeria.[1] The plaintiffs claimed that Pfizer and its researchers violated international standards for the protection of human subjects in clinical trials. In particular, they claimed that Pfizer, the sponsor and conductor of the trials, violated the principle of informed consent by failing to explain the experimental nature of the treatment, that the patients could refuse it, and that other organizations offered conventional treatment free of charge. The plaintiffs criticized Pfizer for failing to provide the best treatment available when it supplied low doses of the control drug ceftriaxone, the drug approved by the FDA for treatment of meningitis in children, and when it failed to monitor the progress of patients in the study. Finally, the plaintiffs questioned the ethics of the company's decision to conduct a clinical trial of a treatment known to cause liver damage in children.

This case presents one of the primary ethical and legal concerns regarding clinical trials in developing nations — how to protect human subjects. Pharmaceutical companies are increasingly testing their products in the developing world and Eastern

1. For the story of the Trovan experiments, see generally Abdullahi v. Pfizer, No. 01 Civ. 8118, 2002 WL 31082956 (S.D.N.Y. Sept. 17, 2002); William DuBois, Note, *New Drug Research, The Extraterritorial Application of FDA Regulations, and the Need for International Cooperation*, 36 VAND. J. TRANSNAT'L L. 161 (2003); Joe Stephens, *Where Profits and Lives Hang in Balance: Finding an Abundance of Subjects and Lack of Oversight Abroad, Big Drug Companies Test Offshore to Speed Products to Market*, WASH. POST, Dec. 17, 2000, at A1.

The case against Pfizer illustrates how pharmaceutical companies fail to protect subjects of clinical trials. During the 1996 meningitis epidemic, Pfizer sent six physicians to the Kano Infectious Disease Hospital in Kano, Nigeria to test the efficacy of Trovan, a potential breakthrough meningitis treatment and possible billion-dollar drug. Though Trovan's class of antibiotics had been shown to cause joint damage in young mammals and had never been tested in children, Pfizer's researchers treated 198 children in Kano. Half were treated with Trovan and half with ceftriaxone, the FDA-approved treatment for meningitis in children. Due to understaffing, Pfizer researchers injected ceftriaxone into children's buttocks, rather than the traditional intravenous method, and administered one-third the regular dose. Medecins Sans Frontieres (MSF), meanwhile, treated patients in the same hospital in the traditional manner. The Pfizer team left Kano after two weeks, leaving no medical records and failing to provide for long-term follow up checks. Nevertheless, Pfizer's final report concluded that Trovan was equally safe and effective for children as ceftriaxone.

The FDA approved Trovan in late 1997; Pfizer's first year sales topped 160 million dollars. The EU, however, refused to approve Trovan for use in children. By mid-1999, reports of serious liver problems led U.S. regulators to recommend that the drug only be prescribed in limited circumstances. Finally, in August 2001, thirty Kano families sued Pfizer under the Alien Tort Claims Act for failure to conform to international standards for the protection of human subjects in clinical trials.

Europe, where "huge pools of human subjects . . . help speed new drugs to the marketplace — [though] they will be sold mainly to patients in wealthy countries."[2] Because their impoverished governments would otherwise be unable to provide medical treatment to their citizens, host countries — African nations in particular — have no legislative protection for subjects of clinical trials.[3] Researchers in such countries, faced with dire medical conditions, understaffed hospitals, language and cultural barriers, and research subjects who would otherwise have no access to medical treatment, thus find it expedient to violate the minimum ethical standards for the protection of human subjects.[4] As noted in *The Washington Post*'s investigation of clinical trials in developing nations, while many trials are conducted carefully, in many instances, "[e]xperiments involving risky drugs proceed with little independent oversight [while] [i]mpoverished, poorly educated patients are sometimes tested without understanding that they are guinea pigs."[5]

In light of this reality, the international research community faces two questions: (1) to what medical standards should pharmaceutical trials in developing nations adhere, and (2) how should these standards be enforced? Part II of this Note addresses the first question, borrowing principles from international agreements and declarations that evince widespread acceptance. The remainder of this Note addresses the second question — how these standards are enforced in clinical trials in developing nations, what the current obstacles to enforcement are, and which model of enforcement will be most useful in the future. Part III discusses the current system of institutional review board and ethical committee review, which those conducting or

2. Stephens, *supra* note 1, at A37; *see also* Sonia Shah, *Globalizing Clinical Research: Big Pharma Tries Out First World Drugs on Unsuspecting Third World Patients,* THE NATION, July 1, 2002, at 23.

3. Benjamin Mason Meier, *International Protection of Persons Undergoing Medical Experimentation*: *Protecting the Right of Informed Consent*, 20 BERKELEY J. INT'L. L. 513, 532–33 (2002).

4. Jay Dyckman, *The Myth of Informed Consent: An Analysis of the Doctrine of Informed Consent and its (Mis)Application in HIV Experiments on Pregnant Women in Developing Countries*, 9 COLUM. J. GENDER & L. 91, 98 (1999) ("Testimony from some of the African participants in these studies offers compelling reasons to doubt the sufficiency of informed consent, regardless of researchers' good intentions; indeed, many participants have expressed confusion about the test.").

5. Stephens, *supra* note 1, at A1.

sponsoring the clinical trials monitor their own actions, as well as the role of national governments in enforcing human rights standards in clinical trials. It also addresses the limited role that private litigation plays in pressuring the pharmaceutical industry to conform to international standards.

In Part IV, this Note discusses steps that the pharmaceutical industry has taken to improve its protection of human subjects in clinical trials, most notably through its recent promulgation of the Pharmaceutical Researchers and Manufacturers Association (PhRMA) Principles. Finally, Part V looks at the recent movement to improve protection of human subjects in clinical trials conducted in the United States and the movement to improve labor conditions in developing countries through the use of accrediting agencies.[6] Drawing on these examples, this Note proposes independent accreditation of those conducting or approving clinical trials, arguing that such accreditation would overcome the inability and unwillingness of foreign governments to police clinical trials, and would enable the United States government and consumers to hold pharmaceutical companies and their institutional review boards accountable for their actions.

II. INTERNATIONAL STANDARDS FOR MEDICAL RESEARCH ON HUMAN BEINGS

Ethical questions abound regarding clinical trials and the extent to which experimental treatments should be used on sick or

6. Non-profit organizations such as the Fair Labor Association have promoted use of factory accreditation and service mark labeling of consumer goods to promote proper labor practices in factories in developing nations that supply goods for retail sale in the United States. Similarly, in the last two years, two non-profit organizations — the Association for the Accreditation of Human Research Protection Program (AAHRPP) and the Partnership for Human Research Protection (PHRP) — have adopted formal accreditation programs for public and private research organizations and for institutional review boards (IRBs) involved in medical research on human participants in the United States. By requiring external, *independent* review, accreditation has improved transparency of the companies' labor rights records, and has given them an incentive to improve their working conditions. Similarly, accreditation of institutional review boards, research centers, and research sponsors by independent accrediting boards could provide these groups with greater incentive to observe international standards for protection of human subjects. Laura Landro, *The Informed Patient: Assessing Safety of Clinical Trials*, THE WALL ST. J., Dec. 5, 2002, at D3.

healthy individuals in developing countries.[7] Despite the ongoing ethical debate, the international medical and legal communities have established various standards addressing the manner in which clinical trials should be conducted. The five most influential guidelines are the Nuremberg Code, the Declaration of Helsinki, Article 7 of the International Covenant on Civil and Political Rights (ICCPR), the Council for International Organizations of Medical Sciences (CIOMS), and the International Council for Harmonization.[8] While the contours and outlines of the standards in these documents are not entirely coterminous, certain minimum features appear to be part of every scheme. Trials must conform to informed consent principles so that participants are aware of the nature of the trial and are free to choose whether or not to participate. Furthermore, the benefits must outweigh

7. Should drugs be tested in countries where the population will never be able to afford the drug? Should experimental treatments be used on sick individuals? Does the provision of free treatment compensate for exposing patients to the risks of untested drugs? More generally, should there be a universal international standard of care, or should trials consider the local standard of care and medical necessity? This last question is addressed in detail by David P. Fidler in *"Geographic Morality" Revisited: International Relations, International Law, and the Controversy over Placebo-Controlled HIV Clinical Trials in Developing Nations*, 42 HARV. INT'L. L.J. 299 (2001). Much of the debate was triggered by Peter Lurie and Sidney Wolfe's 1997 article criticizing as unethical the United States-sponsored AZT trials in sub-Saharan Africa. Peter Lurie & Sidney M. Wolfe, *Unethical Trials of Interventions to Reduce Prenatal Transmission of the Human Immunodeficiency Virus in Developing Nations*, 337 NEW ENG. J. MED. 853 (1997). Those clinical trials tested the short-course AZT regimen, which researchers believed could reduce rates of mother-to-child transmission of HIV, against placebos; because placebos were used as the control, many subjects received no treatment at all. Fidler, *supra*, at 302–03. For a more general discussion of the ethical issues associated with clinical trials in developing countries, see Douglas P. Lackey, *Clinical Trials in Developing Countries: A Review of the Moral Issues*, 68 MOUNT SINAI J. MED. 4 (2001).

8. These standards are both procedural and substantive — requiring, for example, not only that institutional review boards (IRBs) pre-approve trials by institutional review boards (IRBs) before commencement, but also, at a minimum, that trials may only be conducted in a developing nation (a host country) when they cannot reasonably be performed in the country in which the tested product will be sold (the home country). Because of the procedural aspect of these requirements, it is difficult to parse a discussion of what the standards are and whether those standards are enforced; the role of the institutional review boards (discussed in more detail *infra* Part III.A) means that the standards are theoretically self-enforcing. However, for the purposes of this Note, I will assume that the question of enforcement addresses not only whether substantive standards are followed, but also whether procedural standards are followed. Put another way, does a host country review the substantive protections of a trial *and* the procedural protections? Does it monitor IRBs to ensure that they are doing their job or does it simply accept IRB review at face value?

its risks. Finally, certain minimum standards of care are required, and certain vulnerable populations must be protected.

A. INFORMED CONSENT

The foremost protection for human subjects of clinical trials is the principle of informed consent. In general terms, informed consent requires that subjects of trials be adequately informed of the risks and benefits of the trial, of their rights as participants, and their choice whether or not to participate. Informed consent protects research subjects by ensuring that their interests are considered when they are in conflict with those of the researcher and by protecting the subject's "right to bodily integrity" — to "'exercise sovereignty over her body'."[9]

The Nuremberg Code, the first effort by the international community to establish guidelines for medical experiments on humans, first articulated the principle of informed consent.[10] The Nuremberg Code was not a binding treaty but merely an articulation of medical ethics by an American Military Tribunal. Informed consent is the central notion of the Nuremberg Code,[11] and the most widely accepted of its ten basic tenets.[12]

The Nuremberg Code requires that a research subject must be able to "exercise the free power of choice," and must have sufficient knowledge of the nature of the experiment to make an "enlightened decision." The subject should be informed of "the

9. Kevin M. King, Note, *A Proposal for the Effective International Regulation of Biomedical Research Involving Human Subjects*, 34 STAN. J. INT'L L. 163, 174 (1998), *quoted in* Meier, *supra* note 3, at 515.

10. The Nuremberg Code was laid out by the Nuremberg Military Tribunal in *United States v. Karl Brandt.* Meier, *supra* note 3, at 523. *See* II Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No. 10, at 181–82 (1950) (Military Tribunal Case 1, United States v. Karl Brandt et al.) [hereinafter Nuremberg Code]. Following the revelation of the atrocities of Nazi experimentation on human subjects, the Tribunal asserted that medical researchers conducting experiments on humans must abide by ten basic principles — known collectively as the "the Nuremberg Code" — in order to satisfy acceptable norms of medical ethics. Michelle D. Miller, *The Informed-Consent Policy of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Knowledge is the Best Medicine*, 30 CORNELL INT'L L.J. 203, 207–208 (1997).

11. Meier, *supra* note 3, at 523.

12. Informed consent is the only specific provision on human experimentation included in the International Conference on Civil and Political Rights (ICCPR), the only global legally binding treaty to address experimentation on human subjects. For a discussion of the ICCPR, see *infra* note 16 and accompanying text.

nature, duration, and purpose[;] . . . the method and means[;] . . . all inconveniences and hazards reasonably to be expected[;] . . . and the effects upon his health or person which may possibly come from his participation in the experiment."[13]

Notwithstanding these strong statements, while it introduced the concept of informed consent, the non-binding Nuremberg Code "did little to improve the state of human experimentation."[14] The Nuremberg Code was not immediately accepted by the medical community, and was interpreted to apply only to "non-therapeutic" research.[15]

In 1966, the principle of informed consent gained more widespread acceptance when the United Nations incorporated it into the ICCPR. The ICCPR is the only global legally binding treaty to discuss human experimentation. Article 7 of the ICCPR states that "[n]o one shall be subject 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."[16] However, while the ICCPR confers absolute rights, it applies only to state actors and is not self-enforcing. It established informed consent as a principle of international law, but did little more.

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13. Nuremberg Code, *supra* note 10, at Principle 1. The full text of the provision states,

> The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

14. Meier, *supra* note 3, at 524.

15. Research that involved the treatment of the subject was not considered an "experiment" and was not covered by the Code. Miller, *supra* note 10, at 209–210.

16. International Covenant on Civil and Political Rights, *opened for signature* Dec 16, 1966, art. I, S. Exec. Doc. E, 95-2 (1978), 999 U.N.T.S. 171 (entered into force Mar. 23, 1976) [hereinafter ICCPR].

Working on a different track than the political and legal community, the medical community has taken several different approaches to informed consent. The medical community first articulated its own standards in the Helsinki Declaration (the "Declaration"), promulgated by the World Medical Association in 1964 and revised most recently in 2000.[17] The Declaration articulates a vaguer concept of free consent than that of the Nuremberg Code, but adds the condition that consent should "preferably" be obtained in writing.[18] It also distinguishes between "clinical research combined with patient care" and "non-therapeutic clinical research." Only in the latter does the Declaration require free and fully informed consent. In therapeutic research, it does not require consent "where the researcher believes that it is unnecessary or difficult to obtain."[19] The Declaration also relaxes informed consent in cases of legal incompetence, specifying only that consent conform to national as opposed to international standards.[20]

In 1982, the medical community, through the World Health Organization and the Council of International Organization of Medical Societies (CIOMS), published the strictest guidelines to date. The International Ethical Guidelines for Research Involving Human Subjects (the "Guidelines"), most recently amended in 2002, were intended to serve as a model for states drafting legislation concerning the protection of human subjects in medical research.[21]

In sharp contrast to the vague notion of informed consent in the Declaration, the Guidelines identify the specific steps an investigator must follow to obtain consent and the information that

17. Declaration of Helsinki, W.M.A. 52nd Assembly (Oct. 2000), *available at* http://www.wma.net/e/policy/b3.htm [hereinafter "Helsinki Declaration"]. The basic principles of the Declaration are that "it is the duty of the physician to promote and safeguard the health of the people," that "medical progress is based on research which ultimately must rest in part on experimentation involving human subjects," and that "in medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society."

18. The basic principle of informed consent in the Declaration is that "[i]n any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal." *Id.* § B.22.

19. Meier, *supra* note 3, at 526.

20. *Id.*

21. *Id.* at 526–27.

must be conveyed.[22] The Guidelines require that subjects be informed of "the alternative procedures or treatments available; what responsibility, if any, lies with the investigator to provide medical service to the subject; and the provision of free treatment for injuries related to research."[23] Researchers must encourage the participant to ask questions and must update consent if study conditions change.[24]

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has also written model legislation for clinical trial procedures. In 1997, representatives of government and regulatory agencies and private industry from the European Union, Japan, and the United States, Australia, Canada, the Nordic countries, and the World Health Organization (WHO) created the "Good Clinical Practice" (ICH/GCP) standards in order to facilitate "mutual acceptance of clinical data by regulatory authorities" in the European Union, Japan, and the United States by setting common standards for clinical trials involving human subjects.[25]

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22. Rebecca Finkenbinder, *New Recommendations on International Human Research: Can Minimum Standards Prevent the Exploitation of Vulnerable Human Subjects in Developing Countries?*, 21 PENN. ST. INT'L. L. REV. 363, 373–374 (2003). The information the investigator must provide includes (but is not limited to) why the individual is considered suitable for the research; that participation is voluntary and that the individual can withdraw at any time; the purpose of the research and an explanation of how it differs from routine medical care; the expected duration of participation; whether compensation will be provided and if so, in what form; the subject's right to access data; foreseeable risks, pain or discomfort, or inconvenience to the individual (or others); direct benefits; the expected benefits of the research to the community or to society at large; what access participants will have to the drug after research is completed and whether they will be expected to pay for it; currently available alternative treatments; the identity of the sponsors of the research; that treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research and the nature and duration of such care; in what way the subject or the subject's family or dependants will be compensated for disability or death; and that an ethical review committee has approved or cleared the research protocol. Council of International Organization of Medical Societies, International Ethical Guidelines for Research Involving Human Subjects at Guideline 5, *at* http://www.cioms.ch/frame_guidelines_nov_2002.htm (last visited on Feb. 24, 2004) [hereinafter "Guidelines"].

23. Nuffield Council on Bioethics, The Ethics of Research Related to Healthcare in Developing Countries, *available at* http://www.nuffieldbioethics.org/go/ourwork/developing countries/publication_309.html (last visited Apr. 24, 2002).

24. *Id.*

25. Human rights experts criticize the ICH/GCP because of its stated goal of standardizing, rather than improving, protection of human subjects, and because of the degree of industry influence over the standards that it promulgates. It has also been argued that the ICH standards may in fact impose lower informed consent standards than those oth-

The ICH/GCP builds upon the ethical principles of the Helsinki Declaration.[26] It, however, separates the roles and responsibilities of institutional review boards ("IRBs") (which review and approve clinical protocols, generally before trials begin), investigators (those actually conducting the trials), and sponsors (pharmaceutical companies or government agencies).[27] In doing so, the ICH/GCP places most of the burden on the investigator, rather than the sponsor.

The ICH/GCP lays out fairly specific requirements as to the investigator's responsibilities for informed consent, but offers only the barest guidance to sponsors. It specifies requirements as to what information should be relayed to the participant.[28] The GCP specifically forbids coercing or unduly influencing a subject; the subject should have "ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial," and should have all questions about the trial answered.[29]

In contrast to the investigator's role, however, the trial sponsor's responsibilities are limited to "implementing and maintaining quality assurance,"[30] verifying that "subjects are protected," and ensuring that investigators are complying with GCP and regulatory requirements.[31] Further, the sponsor can transfer all

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erwise used in the United States. *See*, *e.g.*, Miller, *supra* note 10. In addition, it has no binding authority as international law. Nonetheless, most industry guidelines find their basis in the document and it serves as the standard for many national governments. *See* International Conference on Harmonization; Good Clinical Practice: Consolidated Guideline; Availability, 62 FED. REG. 25,692, 25,693 (May 9, 1997) [hereinafter "ICH/GCP"].

26. *Id.* at 25,698.

27. *Id.* at 25,697. Other than distinguishing between those conducting the trial and the review committee (or IRB) whose job it is to review research protocol before a trial commences, previous standards did not specify the role of different institutions (such as the hospital or clinic in which the trial takes place, independent doctors hired to run the trial, and the funding organization).

28. The information relayed to the participant should include the purpose of the trial (and both the fact that it involves research and which portions are experimental), the treatment and probability of random assignment, trial procedures, reasonably foreseeable risks, reasonably expected benefits (and if there is no intended clinical benefit), the alternative procedure available and its benefits and risks, that participation in the trial is voluntary, the circumstances and/or reasons under which the subject's participation in the trial may be terminated, and the expected duration of the subject's participation in the trial. *Id.* at 25,698.

29. *Id.* at 25,697.

30. *Id.* at 25,699.

31. *Id.* at 25,702.

trial-related duties to a contract research organization.[32] Thus, while the ICH/GCP creates fairly stringent requirements for informed consent, the daily responsibility for ensuring compliance remains with the investigator. The sponsor of the trial plays a mere supervisory role.

Finally, the United States lays out its informed consent requirements in the Protection of Human Subjects (the "PHS"), a joint policy developed by the FDA and the Department of Health and Human Services. The PHS specifies the eight elements of informed consent required in order for the results of clinical trials to be considered in the FDA drug approval process or for research to receive federal funding.[33] However, under certain circumstances, an IRB may approve a consent procedure that does not include all eight fundamental elements of informed consent. These situations include trials that could not practicably be carried out without the waiver or alteration, occasions when the waiver or alteration would not adversely affect the rights and welfare of the subjects, or research that imposes minimal risks.[34]

> The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. . . based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP.

Id. If a trial is noncompliant, the sponsor should take "prompt action . . . to secure compliance." If noncompliance is serious or persistent, the sponsor must terminate the investigator's participation. *Id.* at 25,702.

32. The sponsor does maintain final responsibility for the compliance of that organization with the requirements of ICH/GCP. *Id.* at 25,699.

33. The eight basic principles which must be communicated to research subjects are (1) a statement that the study involves research, explanation of the purposes and duration of the study, and a description of the procedures, pointing out which are experimental; (2) a description of reasonably foreseeable risks or discomforts; (3) a description of reasonably expected benefits; (4) a disclosure of appropriate alternative treatments; (5) explanation of the level of confidentiality that will be afforded record; (6) if the research involves more than minimal risk, what if any compensation will be provided, and whether treatment for injuries arising will be provided; (7) whom to contact for more information about the research, the subjects' rights, and the contact person in case injury is sustained; and (8) a statement that participation is voluntary, and that the subject may discontinue participation at any time without penalty or loss of benefits. 45 C.F.R. § 46.116(a) (2003) [hereinafter PHS].

34. *Id.* § 46.116(c).

Except in limited circumstances, the PHS does require that consent be obtained in writing.[35]

B. ASSESSING WHETHER A TRIAL SHOULD TAKE PLACE

The Nuremberg Code states that certain research is too risky in relation to its potential benefit, regardless of whether patients would give voluntary informed consent.[36] Thus, it established the principle that those conducting a clinical trial must weigh the benefits to society against the risks to the individual. Because the Nuremberg Code was interpreted by the medical community to apply only to non-therapeutic treatment, however, there was no need to weigh the benefits and risks of trials where the individual was receiving experimental treatment for a condition. The Helsinki Declaration first introduced the idea of extending risk/benefit assessment to therapeutic trials. The Declaration noted that "[m]edical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens" and that "[t]his is especially important when the human subjects are healthy volunteers."[37]

The CIOMS Guidelines were the first to specifically address the risks and benefits that must be weighed when clinical trials are funded by developed countries (the home country) and conducted in developing nations (the host country). The Guidelines require that "research subjects from developing communities not be used in research that could be carried out reasonably well with subjects from developed countries," and that the research be responsive to the health needs of the host community.[38] The Guidelines refer to distributive justice, noting that the benefits and burdens of research should be distributed equally, and that "sponsors of research . . . should [not] take advantage of the rela-

35. *Id.* § 46.117.

36. Jonathan Todres, Note, *Can Research Subjects of Clinical Trials in Developing Countries Sue Physician-Investigators for Human Rights Violations?,* 16 N.Y.L. SCH. J. HUM. RTS. 737, 742–743 (2000); *See* Nuremberg Code, *supra* note 10, at Principles 5 & 6. ("5. No experiment should be conducted when there is [an] *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects. 6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.")

37. Helsinki Declaration, *supra* note 17, at B.18.

38. Guidelines, *supra* note 22.

tive inability of low-resource countries or vulnerable populations to protect their own interests, by conducting research inexpensively and avoiding complex regulatory systems of industrialized countries in order to develop products for the lucrative markets of those countries."[39]

In general terms, the Guidelines require that researchers balance the potential benefits and risks of the trial and minimize the risks. Non-therapeutic trials are permitted if they are justifiable in relation to the expected benefits to society (i.e., the knowledge that they will bring), though this knowledge need not benefit the host society. The risks of therapeutic trials must be justified in relation to the benefits to the *subject*, while the expected benefits of the proposed treatment must at least equal those of the available alternatives.[40]

Most other guidelines do not distinguish between trials taking place in a host country as opposed to a home country, and require a balancing of benefits and risks. For example, the ICH/GCP requires that "before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks."[41] Similarly, the PHS requires that risks to subjects be minimized[42] and be reasonable in relation to anticipated benefits to the subject and to the knowledge that may reasonably be expected to result.[43]

39. *Id.*

40. *Id.* at Guideline 8.

41. ICH/GCP, *supra* note 25, at 25,695.

42. Risks shall be minimized "[b]y using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes." PHS, *supra* note 33, at § 46.111(a)(1).

43. "In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility." *Id.* § 46.111(a)(2).

C. MINIMUM STANDARD OF CARE

In addition to requiring that the expected benefits of a trial outweigh the risks, many guidelines also require a minimum standard of care for participants of a trial. In very vague terms, the Nuremberg Code requires that experiments should be "conducted as to avoid all unnecessary physical and mental suffering and injury."[44] The Helsinki Declaration was the first articulation of a minimum standard of care for participants in therapeutic research. The Declaration 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."[45] No specific standard was set for non-therapeutic research.

Similarly, the CIOMS Guidelines require that research subjects in the control group "should receive an established effective intervention."[46] It is ethically acceptable to use a placebo or no treatment only when there is no "established effective intervention," when "withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms," and when "use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects."[47] The ICH/GCP and the PHS, however, do not prescribe minimum standards of care other than calling for an evaluation of risks and benefits.

III. ENFORCING PROTECTIONS OF HUMAN SUBJECTS OF CLINICAL TRIALS

Despite the existence of national legislation and international agreements on the protection of human subjects in clinical trials,

44. See Nuremberg Code, *supra* note 10.

45. Todres, *supra* note 36, at 747. The most recently revised edition of the Declaration notes that, when combined with therapy, research may only be performed "to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value." Placebos are not ruled out, to the extent that "no proven prophylactic, diagnostic or therapeutic method exists" or the injury treated is a minor harm. Helsinki Declaration, *supra* note 17, §§ C.28–C.29.

46. Guidelines, *supra* note 22.

47. *Id.*

"there is neither widespread nor consistent state practice supporting [the right of free and informed consent]."[48] Other than the ICCPR, which is "hobbled by weak implementation provisions," and has yet to be applied to a single case of medical experimentation,[49] no binding international treaty protects human subjects of clinical trials. Enforcement of ethical standards for clinical trials must come through national governments, from consumer and litigation pressure, and ultimately, from the industry itself. In this section, the various mechanisms of enforcement of clinical trial standards are discussed and their inadequacies analyzed. In particular, this section discusses the role of national governments and private litigation.

A. PEER REVIEW

Institutional review boards are the primary means of enforcing clinical trial standards. IRBs review — and in some instances amend or reject — research protocols for clinical trials. In addition, some IRBs monitor trials for human rights violations on a continuing basis. Often IRBs are the only institutions that attempt to enforce clinical trials standards. However, the effectiveness of an IRB depends on the extent of its ability to prevent, sanction, or suspend clinical trials, and on the ability of the governing regulatory system to ensure that the IRB is performing its job adequately.

The Helsinki Declaration introduced the concept of peer review of research protocol. The Declaration, however, did not grant peer review committees "clear authority" to reject research proposals; committees cannot withhold approval of trial protocols.[50] In addition, the Declaration does not suggest that committees conduct continuous review of research. Rather, committees may only make recommendations for changes to improve protec-

48. Meier, *supra* note 3, at 535.

49. *Id.* at 534 (quoting M. Cheriff Bassiouni et al., *An Appraisal of Human Experimentation in International Law and Practice: The Need for International Regulation of Human Experimentation*, 72 J. CRIM. L. & CRIMINOLOGY 1597, 1657 (1981)).

50. Meier, *supra* note 3, at 526–527. The Declaration helped give rise to the role of institutional review boards and ethics committees in reviewing research proposals and overseeing clinical trials.

tion of human subjects. Thus, the IRBs promulgated by the Helsinki Declaration have been likened to "rubber stamps."[51]

The CIOMS Guidelines, however, greatly increased the power granted to IRBs. Committees were given the authority to reject or approve research proposals.[52] The Guidelines required IRBs to conduct follow-up reviews, and required research in host countries to obtain IRB review in both the host country and the home country.[53] The manner in which IRBs must review research protocols as directed by the Guidelines, however, is vague.[54] In addition, the Guidelines specifically state that IRBs "have no authority to impose sanctions on researchers who violate ethical standards," but may simply withdraw ethical approval, or report "serious or non-continuing compliance" to authorities.[55] The Guidelines also note that sanctions imposed by bodies possessing disciplinary power "should be employed as a last resort."[56] Under the Guidelines, the ability of IRBs to maintain ethical standards rests on the enforcement power of other authorities such as the local government. If a national government does not impose procedural obligations on clinical trials, requiring them to submit to IRB approval, then an IRB in a developing nation has little or no power.[57]

Other than requiring a sponsor to confirm that the IRB has reviewed the trial,[58] the ICH/GCP does not discuss who is responsible for ensuring that IRBs properly review research protocols. It requires that IRBs retain all relevant records and make them available upon request to the "regulatory authority." It does not, however, specify who should review the records nor mention by what standards the IRB's activities should be evaluated.[59] "Regu-

51. Shah, *supra* note 2, at 24.

52. Todres, *supra* note 36, at 749.

53. Meier, *supra* note 3, at 527.

54. The most recent enunciation of the Guidelines instructs IRBs to determine that all proposed treatments are "acceptably safe to be undertaken in humans" and that research is "scientifically sound," to ensure that ethical concerns are "satisfactorily resolved," and to "consider the qualifications of the investigators . . . with a view to ensuring the safe conduct of the trial." IRBs may also forgo these steps if they verify that another "competent expert body" has made these determinations.

55. Guidelines, *supra* note 22, at Comment. on Guideline 2.

56. *Id.*

57. Clinical trials conducted in foreign countries may be used to obtain FDA approval if they conform to the Helsinki Declaration.

58. ICH/GCP, *supra* note 25, at 25,700.

59. *Id.* at 25,696.

latory authorities" are defined as "the authorities that review submitted clinical data and those that conduct inspections."[60] It is unclear whether regulatory authorities located in a home country (such as the Food and Drug Administration ("FDA")) have the power to regulate IRBs located in a host country. Review of the IRBs is left to governmental agencies in the host country which may choose not to review IRB activity at all.[61]

The PHS demands that all research protocols for trials conducted in the United States must be reviewed by an IRB in order to receive federal funding or to be used in the FDA approval process. An IRB may suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements.[62] However, even within the United States, there is little oversight of IRBs. They need not be independent of the institutions whose research protocols they review. According to the FDA, "institutions engaged in research involving human subjects will usually have their own IRBs to oversee research conducted within the institution or by the staff of the institution."[63] Members of the IRB may be compensated for their performance (though compensation may not be linked to favorable review).[64] While at least a certain percentage of IRB members must be unaffiliated with the institution, unaffiliated members need not be present to constitute a quorum.[65] In addition, while the FDA provides for voluntary registration of IRBs, it does not require certification of IRBs or even review of their actions and decisions.[66]

In short, while IRBs serve as the primary compliance monitoring organization in the conduct of clinical research on human subjects, their role is often limited to rubber-stamp approval of

60. *Id.* at 25,695.

61. For a discussion of host country review of clinical trial protocol, see *infra* Part III.C.

62. PHS, *supra* note 33, § 46.113.

63. U.S. FDA, INFORMATION SHEETS: GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS AND CLINICAL INVESTIGATORS at I (1998), *at* http://www.fda.gov/oc/ohrt/irbs/faqs.html (last visited Mar. 3, 2004).

64. *Id.*

65. *Id.* at II.

66. *Id.* at I. *See also* Office for Human Resource Protections, United States Department of Health and Human Services, Registration of an Institutional Review Board (IRB) or Independent Ethics Committee (IEC), *at* http://www.hhs.gov/ohrp/assurances (last visited Aug. 30, 2004).

pre-trial protocols. Many IRBs provide no ongoing review, and most IRBs are not independent from the institutions they are reviewing. Finally, and most significantly, no external review of IRB procedures or decisions exists; even in the United States, IRBs are not themselves subject to review. Thus, the mechanism by which human subjects are protected in clinical trials has neither power nor accountability.

B. NATIONAL REGULATORY AGENCIES: THE ROLE OF THE FDA

Regulatory agencies within developed countries set the standards for trials conducted within their borders. In the United States, for example, the Food, Drug and Cosmetics Act (FDCA)[67] authorizes the FDA to place strict requirements upon pharmaceutical companies applying for marketing approval in the United States. Any clinical trial involving human subjects must be supervised by an IRB, "an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects."[68] Before the trial commences, an IRB reviews research protocols and related materials, such as informed consent documents and investigator brochures. The IRB may also conduct periodic reviews of protocols.[69] Absent a specific waiver by the FDA, trials that have not been properly approved or monitored by IRBs, or that were not conducted in accord with the PHS, will not be allowed to count towards drug approval.[70]

The relatively rigorous requirements the FDA has adopted, however, do not apply outside of the United States, and researchers in foreign trials need only conduct their trials in accordance with the host country's national requirements or the Declaration

67. 21 U.S.C. § 301.

68. U.S. FDA, *supra* note 63, at I.

69. *Id.*

70. The FDA may waive IRB requirements if requested to do so by the sponsor or sponsor-investigator (though it may not waive informed consent requirements). The FDA allows waivers "only where it would be in the best interest of the subjects," such as when an investigational drug is used primarily for the treatment of a serious or immediately life-threatening disease and satisfactory alternate therapies are unavailable. U.S. FDA, INFORMATION SHEETS: GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS AND CLINICAL INVESTIGATORS (1998 UPDATE), DRUGS AND BIOLOGICS, *available at* http://www.fda.gov/oc/ohrt/irbs/drugsbiologics.html (last visited Mar. 3, 2004) (citing 21 CFR § 56.105).

of Helsinki, whichever is stricter.[71] As noted above, the Declaration of Helsinki's IRBs have been likened to a "rubber stamp," and do not provide for ongoing monitoring, while national regulations may be virtually non-existent. In addition, the FDA lacks the power and the resources to ensure that trials are conducted even in accordance with the more lax requirements of developing nations.[72]

C. REGULATION BY GOVERNMENTS OF HOST COUNTRIES

Unfortunately, many host countries simply do not regulate to protect human subjects of clinical trials. This lack of legislation is often intentional; clinical trials provide treatment that the governments of these countries would never be able to afford. For example, "African nations vie to minimize regulation on the conduct of medical research. They fear that legislation, and resulting lawsuits, could have a chilling effect on beneficial research efforts."[73] Malawi, the United Republic of Tanzania, and Zambia, for example, do not have legally binding informed consent procedures, while some countries only require informed consent from a community leader.[74]

Even in countries that require that research proposals be submitted to a review committee, "corruption often prevents these boards from protecting the interests of experimental subjects."[75] Regulators are pressured by drug companies to hasten the research approval process.[76] Even when regulatory bodies do

71. The FDA states that it is not the trial sponsor's responsibility to ensure that a study is conducted in compliance with informed consent and IRB regulations. Rather, "[s]ponsors should rely on the clinical investigator, who assures the sponsor . . . that the study will be reviewed by an IRB." While such information must be made available to the sponsor, an IRB must notify the investigator of the decision to approve, reject, or require modification to a research activity. U.S. Food and Drug Admin., Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators (1998 Update), Sponsor-Investigator-IRB Interrelationship, *available at* http://www.fda.gov/oc/ohrt/irbs/toc4.html (last visited Mar. 3, 2004).

72. Stephens, *supra* note 1, at A1.

73. Meier, *supra* note 3, at 532.

74. *Id.* at 533 n.124.

75. *Id.* at 533.

76. Karen DeYoung & Deborah Nelson, *Latin America Is Ripe For Trials, and Fraud; Frantic Pace Could Overwhelm Controls*, WASH. POST, Dec. 21, 2000, at A1.

punish drug companies for failure to protect human subjects, that punishment is minimal.[77]

Subjects of clinical trials in developing countries lack both of the protections from which their counterparts in the United States benefit; IRBs rubber-stamp approval of research protocols without any recrimination from the governments, and the governments decline to sanction companies for their violations of human rights protections. In many countries, human subjects of clinical trials cannot rely on their own government to protect their rights and interests.

D. THE ROLE OF PRIVATE LITIGATION IN ENFORCING COMPLIANCE

The court system has been a traditional mechanism for enforcing human rights standards. Victims of human rights abuses have sued the perpetrators in both the country in which the abuses took place, and, through the use of the Alien Tort Claims Act ("ATCA")[78] and the principle of universal jurisdiction, in the courts of the United States and other developed countries. However, due to the inhospitability of the courts in host countries, and the Supreme Court's recent curtailment of the ATCA in *Sosa v. Alvarez-Machain*,[79] private litigation is an unlikely means for curtailing abuses of human subjects in clinical trials.

The ATCA is a section of the 1789 Judiciary Act which states that "[t]he district courts shall have original jurisdiction of any civil action by an alien for a tort only, committed in violation of the law for nations or a treaty of the United States."[80] Forgotten

77. Joe Stephens, *Testing Tidal Wave Hits Overseas; On Distant Shores, Drug Firms Avoid Delays and Scrutiny Series: The Body Hunters: Overwhelming the Watchdogs*, THE WASH. POST, Dec. 18, 2000, at A1 ("[Bulgaria's entire drug testing police] force consists of one person, Ilian Ivanov, a bearded thirty-one year-old who keeps chilled whiskey at the ready for office visitors. Ivanov earns about $100 a month. He simultaneously protects Bulgarians from ill-advised drug tests and promotes Bulgaria as a test site. Ivanov persuaded Eli Lilly and 15 other companies to sponsor the Borovets conference. And he said he one day hopes to work in the industry he now oversees, just as his predecessor did. But Ivanov insisted companies and doctors know where he draws the line. He said he cracked down last year on a pair of Bulgaria's most respected drug researchers for conducting an experiment without government approval. Their fine: $10.").

78. 28 U.S.C. § 1350.

79. Sosa v. Alvarez-Machain, 124 S. Ct. 2739 (2004).

80. 28 U.S.C. § 1350.

for almost 200 years, a federal appellate court first recognized the ATCA as a viable basis for relief in 1980.[81] Since then groups such as the Center for Constitutional Rights, who have sued multinational corporations including Shell and Unocal for their role in human rights abuses in Nigeria and Burma, have used the act as the basis for impact litigation.[82] Similarly, in August 2001, thirty Nigerian families sued Pfizer under the ATCA for the clinical trials it conducted in Nigeria during the 1996 meningitis epidemic.[83]

The Supreme Court's recent ruling in *Sosa v. Alvarez-Machain*, however, has severely limited the claims which may be made under the statute.[84] *Sosa* requires that "federal courts should not recognize claims under federal common law for violations of any international law norm with less definite content and acceptance among civilized nations than the 18th-century paradigms familiar when [the ATCA] was enacted."[85] The courts should only recognize such claims as "violation of safe conducts, infringement of the rights of ambassadors, and piracy."[86] At the time that *Sosa* was decided, the case against Pfizer was still

81. Filartiga v. Pena-Irala, 630 F.2d 876 (2d Cir. 1980); s*ee also* Kadic v. Karadzic, 70 F.3d. 232, 239–40 (2d Cir. 1995) (extending ATCA claims to torts committed by private actors).

82. Wiwa v. Royal Dutch Petroleum Co., 226 F.3d 88 (2d. Cir. 2000); John Doe v. Unocal Corp., 963 F.Supp. 880 (C.D. Cal. 1997).

83. Abdullahi v. Pfizer, No. 01 Civ. 8118, 2002 WL 31082956, at *1 (S.D.N.Y. Sept. 17, 2002).

84. *Sosa*, 124 S. Ct. at 9. The ATCA had come under attack from critics who consider the statute as it has been interpreted as unconstitutional and detrimental to American foreign policy and economic interests abroad. *See generally* Philip I. Blumberg, *Asserting Human Rights Against Multinational Corporations Under United States Law: Conceptual and Procedural Problems*, 50 AM. J. COMP. L. 493 (2002); Michael Dwayne Pettyjohn, *"Bring Me Your Tired, Your Poor, Your Egregious Torts Yearning to See Green": The Alien Tort Statute*, 10 TULSA J. COMP. & INT'L L. 513 (2003). Though the Ninth and Eleventh Circuits followed *Filartiga*, two justices on the D.C. Circuit criticized the decision in concurring opinions.

85. *Sosa*, 124 S. Ct. at 2761.

86. *Id.* at 2756. Even in the Second Circuit, the requirements for proving an ATCA claim were high. Plaintiffs had to assert a tort that was a violation of the "law of nations," that the defendant was sufficiently involved with a government to be considered a state actor or that the tort was so egregious as to fall under the small category of harms "of universal concern," and that there was no adequate alternate forum in which the case may be adjudicated. The "law of nations" was limited to that which states universally abided by "out of a sense of legal obligation" and that which was of "mutual" not just "several" concern of the states. Flores v. Southern Peru Copper Corp., 343 F.3d 154, 155 (2d Cir. 2003).

pending.[87] Given that the first time that the international community recognized the need to protect human subjects of clinical trials was after World War II — indeed, given that clinical trials did not exist in the eighteenth century, in the manner in which we recognize them — it is almost certain that under the *Sosa* ruling, Pfizer's conduct will be held not actionable.

Universal jurisdiction, a principle by which countries allow for suits by non-nationals against non-nationals for "international crimes," presents another theoretical avenue for private litigation. It was a relatively limited principle until 1993,[88] when Belgium adopted a universal jurisdiction law allowing its courts to try non-nationals for crimes that had no link to Belgium, even if those persons were not present in Belgium at any point.[89] To this date the Belgian law has been primarily applied to crimes allegedly committed by state actors or by non-state actors "who have acted within the framework of systematic violations for which the state is responsible,"[90] and has been restricted to what are considered "international crimes," such as genocide, torture and persecution.[91] Given the controversial nature of the currently limited application of the law, it seems unlikely that generalized universal jurisdiction laws will be applied to multinational corporations violating international standards for human protection in clinical trials.

Litigation in the host countries is often unproductive for several reasons. First, developing nations often lack legislation de-

87. Abdullahi v. Pfizer, 77 Fed. Appx. 48, 51 (2d. Cir. 2003). The Second Circuit had reversed the District Court's dismissal on forum non conveniens grounds, while the District Court had denied Pfizer's 12(b)(6) motion to dismiss for failure to state a claim. The District Court noted that the conduct alleged by the plaintiff was not a violation of "universal concern" for which a private party may be liable, but that the plaintiff sufficiently alleged that Pfizer and the Nigerian government were joint participants in the trials such that Pfizer was a de facto state actor. Neither court had addressed whether the conduct alleged — failure to protect the rights of human subjects of medical experimentation — qualified as a violation of "customary international law," such that it was actionable under the Second Circuit's pre-*Sosa* ATCA standards.

88. Henry J. Steiner, *Three Cheers for Universal Jurisdiction — Or is it Only Two?*, 5 THEORETICAL INQUIRIES L. 199 (2004).

89. Malvina Halberstam, *Belgium's Universal Jurisdiction Law: Vindication of International Justice or Pursuit of Politics?*, 25 CARDOZO L. REV. 247 (2003). Ariel Sharon, Yasser Arafat, Fidel Castro, George H.W. Bush and Saddam Hussein have all been the subject of proceedings (though many of these cases were not actively pursued). Steiner, *supra* note 88, at 229.

90. *Id.* at 200.

91. *Id.* at 208.

signed to protect human subjects, or fail to enforce what legislation is in place.[92] Even where national laws protect subjects by affording them a cause of action under negligence, medical malpractice, or personal injury law, plaintiffs are unable to find relief in the courts. While there is little evidence available as to the success of such litigation, the Second Circuit analysis in its remanding of *Abdullahi* is enlightening.

In *Abdullahi*, the Second Circuit remanded the case to the District Court for further analysis of the *forum non conveniens* motion.[93] The ATCA requires that the plaintiff show that absent litigation in the U.S., he is "highly unlikely to obtain basic justice."[94] A *forum non conveniens* dismissal is usually granted if the plaintiff has standing in another jurisdiction.[95] Though Pfizer was subject to service of process in Nigeria and Nigerian law recognizes negligence, medical malpractice, and personal injury claims, the Second Circuit recognized the plaintiffs' argument that the Nigerian court system was too corrupt to be considered an adequate alternative forum.[96] The court noted that the plaintiffs had submitted "a number of State Department and United Nations" reports that included general observations about the corruption in Nigeria's judiciary.[97] The court also addressed the dismissal of the parallel action filed in Nigeria,[98] where the only official explanation was that the judge presiding had refused jurisdiction for "personal reasons."[99]

Those wishing to sue a corporation for violation of clinical trial standards may, therefore, lack any forum in which their claims can be heard. Litigation in the home country is often ineffective, and the United States court system may no longer be available after *Sosa*.

92. *See supra* Part III.C.
93. Abdullahi v. Pfizer, 77 Fed. Appx. 48 (2d Cir. 2003).
94. Abdullahi v. Pfizer, No. 01 Civ. 8118, 2002 WL 31082956, at *23 (S.D.N.Y. Sep. 17, 2002) (citing Cabiri v. Assasie-Gyimah, 921 F. Supp. 1189, 1199 (S.D.N.Y. 1996)).
95. *Id.* at *21.
96. *Abdullahi,* 77 Fed. Appx. at 52 (citing *Abdullahi*, 2002 WL 31082956, at *7).
97. *Id*.
98. *Id.*
99. *Id.*

E. MARKET PRESSURE ON THE PHARMACEUTICAL INDUSTRY

While government regulation and litigation may not result in compliance with minimum standards for protection of human subjects of clinical trials, market pressure and media attention may compel the pharmaceutical industry to pay greater attention to its design of clinical trials in developing nations.

1. *Human Rights Violations by Multinational Corporations: Public Pressure and Industry Response*

In the 1990s, consumers, investors, and the media turned their attention to human rights abuses by multinational corporations in developing nations. In addition to the traditional activist groups, institutional investors, the media, consumers, and shareholders began to pressure corporations to adopt and comply with corporate codes of conduct. Many are familiar with media campaigns and consumer boycotts against such corporations as Nike and Kmart (due to its Kathie Lee Gifford line of clothing), which allegedly manufactured their products in sweatshops employing child labor, paying substandard wages, and violating other standards for labor rights.

In addition to consumer activism, multinational corporations found themselves confronted with shareholder activism. Aided in part by the internet — which provided a cheap and effective means of mass communication — common shareholders began to form coalitions to pressure corporations to change their practices.[100] Contemporaneously, institutional investors began to play a more activist role, becoming a powerful force for promoting corporate compliance with human rights standards. For example, CalPERS, the California Public Employees' Retirement System, now invests only in firms based in developed nations that obey the Global Sullivan Principles, a code of conduct regulating U.S. corporate abuses abroad.[101] CalPERS also screens all "emerging

100. ExxonMobil, for example, has been very susceptible to pressure from shareholder coalitions. Mark B. Baker, *Tightening the Toothless Vise: Codes of Conduct and the American Multinational Enterprise*, 20 WIS. INT'L L.J. 89, 129 n.240 (2001). *See, e.g.*, CorpWatch, *at* http://www.corpwatch.org, and SocialFund, *at* http://www.socialfund.org.

101. Robert Collier, *State Employee's Pension Fund Flexes its Muscle Around the World,* THE SAN FRANCISCO CHRONICLE, July 21, 2002, at A12; *see also* Global Sullivan Principles, *at* http://globalsullivanprinciples.org/principles.htm (last visited Aug. 10, 2004).

markets" investments to ensure that they are not supporting human rights violations.[102]

In response to public, shareholder, and media pressures, certain industries adopted accreditation or certification programs, whereby corporate codes of conduct are enforced by a product-labeling scheme.[103] Those who subscribe to the program and are accredited may place a label on their products indicating to consumers the company's adherence to human rights standards.

The Free Labor Association ("FLA"), created in 1998 by the Apparel Industry Partnership ("AIP"), allows such apparel manufacturers such as Nike and Levi Strauss to declare that the factories that supply their goods maintain a minimum standard of human rights (the Workplace Code of Conduct). Signatories to the Free Labor Association must be monitored for compliance with the code by "external independent monitors." The monitoring function may be performed by non-profit nongovernmental organizations ("NGOs"), or by traditional for-profit auditing agencies (such as Price Waterhouse Coopers), which in turn must be certified by the FLA.[104] Once certified, signatories can attach a service mark to their applicable brands, and may advertise using the mark "so that consumers may strategically use their purchases to reward companies endeavoring to improve overseas labor conditions."[105]

An industry's decision to self-regulate in such a manner has been called a "combination of altruism and enlightened self-interest."[106] Since self-interest tends to dominate this balance, companies and industries will only accept or promote such programs when those labeling schemes influence consumer and investor choices. As noted by Robert Liubicic, "the linchpin neces-

102. CalPERS decided in 2002 to divest from Indonesia, Malaysia, the Philippines, and Thailand. William Baue, *Debate Continues Over Effects of CalPERS' Divestment from Emerging Market Countries,* SocialFunds.com newsletter, *available at* http://www.socialfunds.com/news/article.cgi (May 7, 2002) (last visited Mar. 2, 2004).

103. Baker, *supra* note 100, at 129.

104. *Id.* at 133–134; Robert J. Liubicic, *Corporate Codes of Conduct and Product Labeling Schemes: The Limits and Possibilities of Promoting International Labor Rights Through Private Initiatives*, 30 LAW & POL'Y INT'L BUS. 111, 125–126 (1998).

105. Maria Gillen, Note, *The Apparel Industry Partnership's Free Labor Association: A Solution to the Overseas Sweatshop Problem or the Emperors' New Clothes?*, 32 N.Y.U. J. INT'L L. & POL. 1059, 1062–63 (2000).

106. Baker, *supra* note 100, at 114 (quoting Dominic Bencivenga, *Corporations Weigh Benefits of Voluntary Plans*, N.Y.L.J., July 13, 1995, at 5).

sary to the adoption of a code or labeling scheme by a U.S. MNC [multinational corporation] [is] corporate and/or brand image."[107] Consumer pressure can only affect those companies whose sales are premised on their reputation. Brands such as Starbucks, Nike, The Gap, Levi Strauss, and Kathie Lee Gifford's Kmart line of clothing have been particularly vulnerable.[108] Investor pressure is felt more strongly by those corporations with a large base of conscientious institutional investors, or when companies commit particularly egregious violations of human rights.[109]

2. *Pressuring the Pharmaceutical Industry*

While consumers could pressure pharmaceutical companies to improve protection of human subjects in clinical trials as they have Nike, Levi Strauss, and other brand name manufacturers, there are fundamental differences between these industries that make this strategy difficult. Competition among pharmaceutical companies differs drastically from the competition among apparel manufacturers. Under the current United States patent system, a new chemical compound (i.e. a new drug) can be patented for twenty years from the date of a patent application.[110] No other manufacturer may use, make, or sell that compound until the patent has expired. Unless the patent is invalid in some way, companies wishing to compete with that drug must develop their own competing drugs from scratch. To the extent that a drug is the only one of its kind on the market the manufacturer has a de facto monopoly. While it is easy to ask consumers to boycott Nike

107. Liubicic, *supra* note 104, at 115.

108. *Id.*

109. After learning that Chevron was implicated in the murder of Nigerian villagers, shareholders, supported by a socially conscious investment firm, passed a resolution requiring the company to revise its code of conduct. Cristina Baez et al., *Multinational Enterprises and Human Rights*, 8 U. MIAMI INT'L & COMP. L. REV. 183, 390 (2000).

110. The length of a patent term in the United States had been seventeen years from the date of issuance. However, the recent accords concerning trade-related aspects of intellectual property rights ("TRIPs") sought to harmonize international patent standards — thus all World Trade Organization members and TRIPs signatories must now protect patents for twenty years from the date of filing. More significantly, however, TRIPs required that all countries provide patent protection to pharmaceuticals. Until TRIPs, many countries had provided little or weak protection to drugs. While countries may exclude from patent protection inventions deemed necessary to "protect ordre [sic] or public morality," countries may not declare pharmaceuticals ineligible for patent protection. MARTIN J. ADELMAN ET AL., CASES AND MATERIALS ON PATENT LAW, 17–18, 59–60. (2003).

sneakers because they are made in a sweatshop in Vietnam, and instead buy more expensive New Balance sneakers, it is difficult to ask consumers suffering from pneumonia to refuse to buy Zithromax, Pfizer's short-course antibiotic, because Pfizer trials in Africa do not follow proper informed consent procedures when these consumers have no equivalent alternative at any price.

Lack of competition is less of a problem among drugs whose patents have expired and which may be manufactured by "generic" manufacturers such that there are multiple manufacturers on the market. Unfortunately, because the number of clinical trials required in order to obtain marketing approval for a generic drug is so low, the impact of such consumer-driven policy would be minimal.[111]

While the investing public may at some point prove to be an effective tool to improve protection of human subjects of clinical trials, most social investment groups have not specifically recognized protection of human subjects of clinical trials as an issue. Rather, these groups have focused on global corporate accountability as a whole (supporting such programs as the Sullivan principles), or in the case of the pharmaceutical industry, its response to the AIDS pandemic in Africa. These groups, however, are beginning to take notice. As a result, Bristol-Meyers Squibb has proudly announced in its corporate governance reports that its protections for human subjects of clinical trials are approved by Calvert.[112]

In addition, the highly public nature of the pharmaceutical industry makes it vulnerable to media attention. In 2000, *The Washington Post* ran a series of eight articles, entitled "The Body

111. In the United States, once a patent has expired, or it has shown to be invalid, generic manufacturers may gain FDA approval to market their drugs through an Abbreviated New Drug Application ("ANDA"). ANDAs do not require human clinical data to establish safety and efficacy; rather, the applicant must prove that their product is the "bioequivalent" — i.e. that it performs in the same manner as the original drug. This proof can be accomplished with minimal human research (often less than 40 human volunteers are needed). Food and Drug Administration, Center for Drug Evaluation and Research, Abbreviated New Drug Application Process for Generic Drugs, *at* http://www.fda.gov/cder/regulatory/applications/anda.htm (last updated Dec. 30, 2003).

112. Bristol Meyers Squibb, Sustainability Report 2003: Sustaining Bioethics, *at* http://www.bms.com/static/ehs/report/data/s03p28.html (last visited Aug. 21, 2004). Calvert Group is a leader in socially responsible investing, offering socially responsible mutual funds, financial services for individual and institutional investors, and information on socially responsible investing. *See* Calvert Online, About Calvert.com, *at* http://www.calvert.com/aboutindex.htm (last visited Sep. 14, 2004).

Hunters" on the problems in international clinical trials. Joe Stephens' article in particular highlighted the Trovan trials in Nigeria, and was one of the impetuses behind the *Abdullahi* case.[113]

Finally, the consolidated nature of the pharmaceutical industry may make it susceptible to activist pressure if pressure points can be found. In recent years, the pharmaceutical industry has consolidated into a small number of mammoth companies that fund and oversee the vast majority of privately funded research and development. In the 1970s, none of the more than 100 pharmaceutical research companies of significant size could claim a global presence. Today, there are only a dozen major pharmaceutical companies around the world.[114] Because there are so few large pharmaceutical companies, and because they control so much of the world's privately funded clinical trials, encouraging even one major company to insist upon accreditation would itself have far-reaching effects. In addition, the highly competitive nature of the pharmaceutical industry means that the actions of one company are frequently mimicked by its competitors. Thus, convincing one company to accept a new method of compliance could revolutionize the industry.

IV. INDUSTRY RESPONSES TO MARKET PRESSURE

Despite the lack of enforcement mechanisms in international treaties regarding informed consent procedures, and the inability of the FDA and the European Union to regulate clinical trials in developing countries — and perhaps in response to litigation, media, and market pressures — the pharmaceutical industry has begun to make policy statements and adopt standards in regards to human rights in clinical trials abroad. In 2002, the Pharma-

113. *See* Stephens, *supra* note 1; DeYoung & Nelson, *supra* note 76.

114. Many of the current pharmaceutical companies consist of consolidations of the many smaller companies. Glaxo Smith Kline, for example, is comprised of Glaxo, Wellcome/Burroughs Wellcome, and SmithKline and Beecham. Alan Williams, *Consolidation Revisited*, 8 J. OF COMM. BIOTECHNOLOGY 130 (2001). As recently as February 2004, Sanofi-Synthelabo offered a bid of $60 billion dollars in a hostile takeover attempt of Aventis. In 2002, Pfizer, at that point the largest seller of prescription drugs in the United States, became the world's largest pharmaceutical company by purchasing Pharmacia for close to $63 billion dollars. Gordon Platt, *The Americas: Pharmaceutical Industry Continues to Consolidate*, 16 GLOBAL FIN. 22 (2002); Andrew Ross Sorkin & Gardiner Harris, *Sanofi Is Ready to Announce Aventis Bid*, N.Y. TIMES, Jan. 26, 2004, at A6.

ceutical Research and Manufacturing Association (PhRMA) published "Principles on the Conduct of Clinical Trials,"[115] incorporating many of the requirements set forth in the ICH/GCP guidelines.[116] Similarly, individual pharmaceutical companies have begun to set policies on clinical trial standards. Pfizer has formulated a "Policy on Global Clinical Trial Standards," while Bristol Meyers Squibb, through its Pharmaceutical Research Institute, has established a clinical trials policy supported by Calvert.[117] However, the standards adopted by the industry remain voluntary, and compliance with these standards is not disclosed to the public.[118]

A. PHRMA PRINCIPLES ON CONDUCT OF CLINICAL TRIALS AND COMMUNICATION OF CLINICAL TRIAL RESULTS

In 2002, the Pharmaceutical Research and Manufacturer's Association ("PhRMA") adopted a set of voluntary standards entitled, "Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results" (the PhRMA Principles). The PhRMA Principles specifically note that responsibility for ensuring that clinical trials are conducted according to legal and ethical standards lies not just with pharmaceutical companies, but also with other entities involved in clinical research. These entities include regulatory agencies, investigative site staff and medical professionals serving as clinical investigators, IRBs, hospitals, and other institutions where research is conducted. While the PhRMA Principles promote the use of IRBs to approve proposed trial protocols and encourage monitoring of trials by "appropriately trained and qualified individuals," these standards are voluntary. PhRMA has no means of assessing whether pharmaceu-

115. PhRMA, PRINCIPLES ON THE CONDUCT OF CLINICAL TRIALS (2002), *available at* http://www.phrma.org/publications/policy//2002-06-24.430.pdf (last visited Sep. 30, 2004).

116. *See supra* Part II.A.

117. Pfizer, Policy on Global Clinical Trial Standards, *at* http://www.pfizer.com/are/about_public/mn_about_ethical_trials_standards.html (last visited Aug. 21, 2004); Bristol Meyers Squibb Sustainability Report 2003: Sustaining Bioethics, *supra* note 112.

118. While the companies broadcast their standards on their websites, they do not publish statistics or reports indicating their own rates of compliance. *See, e.g.*, Commitment to Conducting Ethical Clinical Trials, *supra* note 117; Bristol Meyers Squibb Sustainability Report 2003: Sustaining Bioethics, *supra* note 112.

tical companies, or other entities involved in clinical research, abide by these standards.

For the most part, the PhRMA Principles do not promulgate new standards, but instead refer to those set forth in the Declaration of Helsinki and ICH/GCP, as well as in national and U.S. Food and Drug Administration requirements. Thus, the preamble to the discussion on the "Conduct of Clinical Trials" notes,

> We conduct clinical trials in accordance with applicable laws and regulations, as well as locally recognized good clinical practice, wherever in the world clinical trials are undertaken. When conducting multinational, multi-site trials, in both the industrialized and developing world, we follow standards based on the Guideline for Good Clinical Practice of the International Conference on Harmonization.[119]

While trials conducted in more than one country should follow ICH/GCP practices, those confined to a single country, even if funded by another country, must only conform to local standards. As previously noted, these local standards may be virtually nonexistent.

PhRMA's only discussion of trials conducted in the developing world merely requires that "sponsors collaborate with investigators and seek to collaborate with other relevant parties such as local health authorities and host governments to address issues associated with the conduct of the proposed study and its follow-up."[120]

PhRMA's standards require that each clinical trial must be reviewed by an IRB with independent decision-making authority to disapprove or require changes to the proposed protocol, and that trials must be monitored by "appropriately trained and qualified individuals," to verify compliance with good clinical practices.[121] However, if a pharmaceutical company discovers that an investigator is significantly deficient in any area, it may "either work with the investigator to obtain compliance or discon-

119. PhRMA, *supra* note 115, at 2–3.
120. *Id.* at 12.
121. *Id.* at 9, 11.

tinue the investigator's participation in the study, and notify the relevant authorities as required."[122]

While the articulation of these goals by the leading industry group is a positive step, PhRMA's statement itself does little to ensure improved protection of human subjects in clinical trials. It does not provide for any independent oversight of IRBs, nor does it articulate what constitutes "appropriately trained and qualified individuals" to verify compliance with ICH/GCP. Most notably, PhRMA does not provide any means by which to sanction those manufacturers and researchers whose studies do not comply with ICH/GCP or national standards.

B. INDIVIDUAL CORPORATE CODES OF CONDUCT

Individual pharmaceutical companies have begun to address their own standards for clinical trials. Pfizer, perhaps in response to the attention that it received from *Abdullahi v. Pfizer*,[123] published a statement entitled "Pfizer's Commitment to Conducting Ethical Clinical Trials."[124] In the statement, Pfizer claims that its research is conducted in accordance with ethical guidelines such as the Nuremburg Code, and that it adheres to the ICH/GCP and the PhRMA Principles. The statement further notes that internal procedures "ensure compliance with these standards."[125] Pfizer has also created policy statements on global clinical trial standards, compensation to human research, compassionate use of unapproved Pfizer drugs, and other issues.

In its statement on global clinical trial standards, Pfizer specifically mentions two of the major problems in conducting trials in developing nations — social and cultural differences, and the lack of adequate laws by national governments — noting that these problems may necessitate implementing additional measures to ensure protection of all trial participants.[126]

122. *Id.*

123. For a discussion of the case, see *supra* Part III.D.

124. Pfizer, Pfizer's Commitment to Conducting Ethical Clinical Trials, *at* http://www.pfizer.com/are/about_public/mn_about_ethical_trials.html (last visited Mar. 4, 2004).

125. *Id.*

126. *See* Pfizer, *supra* note 117.

All Pfizer studies must be reviewed by an IRB/EC, or, where a country "lacks adequate human subject protection/IEC/IRB infrastructure, the study should undergo ethical review in both the host and Pfizer-sponsoring country (i.e., U.S., U.K., or Japan), where possible."[127] However, while a review in the sponsoring country will evaluate protocol and clinical trial design and informed consent, it will not oversee or monitor trials.[128]

The Pfizer statement itself adds little substance to trial standards. In relation to informed consent, Pfizer merely requires that procedures meet "local custom and culture in developing countries."[129] Pfizer states only that it will provide "the best standard of care for the control group that is medically and ethically appropriate for the study," and that trial protocol should assess the "appropriateness, relevance, and feasibility of continuing to provide the study drug at the conclusion of the clinical trial."[130]

Though Bristol Meyers Squibb ("BMS") does not publish its specific policy on clinical trials, in its 2003 Sustainability Report BMS discusses practices for clinical trials and the role of its Bioethics Committee. BMS claims that the committee is addressing "informed consent, and the readability of the forms, as well as informed consent made on behalf of children.[131] BMS further notes that its policies are "in a state of continuous reconsideration," and claims that "[a] bioethics training program has been developed that will be mandatory for all those involved in clinical research and development around the world."[132]

AstraZeneca, in its "Bioethics Statement," claims that to comply with many of the generally accepted standards:

> Volunteers/patients in AstraZeneca studies will be given full, truthful and understandable information, in accordance with the general principles set out in the Declaration of Helsinki and in the International Conference on Harmonization Guidelines for Good Clinical Practice, about the aim of the

127. *Id.*
128. *Id.*
129. *Id.*
130. *Id.*
131. Bristol Meyers Squibb, *supra* note 112.
132. *Id.*

> study . . . details of the study procedures . . . benefits and risks . . . [and] freedom to withdraw from the study at any time without giving a reason.

AstraZeneca claims to have a "Standard Operating Procedure," to ensure that these requirements are met, and requires that consent should "normally" be in writing.[133] AstraZeneca, however, does not discuss how it polices its policies or ensures that investigators comply with them.

None of these industry-articulated standards provides any basis for ensuring compliance. IRBs, investigators, and the pharmaceutical companies may have to account to one another under voluntary compliance standards, but they do not have to account to anyone outside the industry, nor do they make available to the public the rates of compliance or problems in the clinical trial process. What information they do make public is at their own discretion. In short, there is no structural transparency in the attempts by the pharmaceutical industry to ensure protection of human subjects of clinical trials.[134] Transparency as to labor rights abuses, however, has been created in the apparel industry through the use of product labeling and factory accreditation to enforce compliance with corporate codes of conduct.[135] Accreditation could serve a similar purpose for the pharmaceutical industry and human subject clinical trials.

V. ACCREDITATION OF ORGANIZATIONS CONDUCTING CLINICAL TRIALS

Within the United States, consumers have begun to articulate their growing distrust of the institutional review board peer-review system for ensuring protection of human subjects of clinical research. As a result of "widespread media attention," litigation, and a "heightened public awareness of research-related

133. AstraZeneca, Bioethics Policy 10, *available at* http://www.astrazeneca.com/sites/7/imagebank/typeArticleparam11115/bioethics_policy_2003_final.pdf (last visited Mar. 4, 2004).

134. While the pharmaceutical industry may release information about its compliance with its own standards, this ad hoc transparency — "transparency by grace" — is not an ineffective means of policing corporate activity. William B.T. Mock, *Corporate Transparency and Human Rights*, 8 TULSA J. COMP. & INT'L. L. 15, 18 (2000).

135. *See supra* Part III.E.1.

deaths," the pharmaceutical industry has begun to reform its oversight of clinical trials in the United States.[136] In addition, two nongovernmental organizations, the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) and the Partnership for Human Research Protection (PHRP) have developed accreditation programs designed to ensure compliance with human protection standards by various institutions that engage in research on human participants. These accreditation boards mirror the trend of accreditation and labeling as a means of protecting labor rights in factories in developing nations that supply multinational corporations with consumer products. If applied to clinical trials in developing nations, the accreditation boards may provide a mechanism for protecting human subjects of clinical trials.

A. ACCREDITATION IN THE UNITED STATES

Currently, two organizations in the United States accredit clinical trials and the various institutions involved in the clinical trial process: the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) and the Partnership for Human Research Protection (PHRP). The organizations have slightly different approaches to the accreditation process. Their programs are discussed in more detail below. Both the AAHRPP and the PHRP are voluntary within the United States. PHRP just accredited its first organization, the Patient Advocacy Council in Mobile, Alabama, in January, 2004.[137] The AAHRPP, which began accreditation in 2003, has conferred full accreditation status on twelve organizations and conditional accredited status on two.[138] The PHRP, which began accreditation in 2004, has ac-

136. Stephen A. Bent, *Certification for Clinical Trials*, PHARMACEUTICAL EXECUTIVE, June 1, 2003, at 28.

137. PHRP, Organizations Accredited by PHRP, *at* http://www.phrp.org/ (last visited Aug. 10, 2004).

138. The institutions accredited include IRBs, universities, hospitals and research centers. The institutions are: the Copernicus Group IRB, Fox Chase Cancer Center, Washington University in St. Louis, Chesapeake Research Review Inc., Dana-Farber/Harvard Cancer Center, Cedars-Sinai Medical Center, Catholic Medical Center, Baylor Research Institute, Hunter Holmes McGuire Veterans Affairs Medical Center, New England Institutional Review Board, University of Iowa, and Western Institutional Review Board. AAHRPP, Accredited Organizations, *available at* http://www.aahrpp.org/accredited_organizations.htm (last visited Aug. 10, 2004).

credited seven organizations.[139] Though certain members of the pharmaceutical industry have taken notice and have advocated embracing accreditation, the industry has yet to act as a whole.[140] Nonetheless, these programs may provide a model on which to build a program to accredit the institutions involved with clinical trials in developing nations.

1. *The Association for the Accreditation of Human Research Protection Programs, Inc. ("AAHRPP")*

The AAHRPP, a nonprofit organization itself founded by a consortium of seven organizations, offers accreditation to institutions engaged in research involving human participants.[141] The AAHRPP reviews academic institutions, hospitals, government agencies, private corporations, and independent review boards.[142] While it focuses heavily on American entities, it will review international entities for eligibility on a case-by-case basis.

The AAHRPP's accreditation process involves self-assessment, on site assessment, a scheduled visit during which an AAHRPP team evaluates the program in respect to AAHRPP's standards, and a review by the AAHRPP's Council on Accreditation.[143] Or-

139. These organizations include IRBs, hospitals, and research institutions: the Chesapeake Research Review, Inc., Aurora Health Care, Inc., National Jewish Medical & Research Center, Biomedical Research Alliance of New York IRB, Essex Institutional Review Board, Hartford Hospital, and Patient Advocacy Council, Inc. Organizations Accredited by PHRP, *at* http://www.phrp.org/e3front.dll?durki=6856&site=54&return=6157 (last visited Aug. 10, 2004).

140. Bent, *supra* note 136. "[A]s increased publicity and research-related lawsuits bring more scrutiny to human research programs, the pressure for accreditation will increase as well. The pharma industry should get on board now and support legislative efforts that mandate accreditation or at least provide recognition and incentives for research organizations and IRBs that seek and achieve such status."

141. The AAHRPP was founded by the Association of American Medical Colleges, the Association of American Universities, the Consortium of Social Science Associations, the Federation of American Societies for Experimental Biology, the National Association of State Universities and Land Grant Colleges, the National Health Council, and Public Responsibility in Medicine and Research. AAHRPP, Founders, *at* http://www.aahrpp.org/founders.htm (last visited Aug. 29, 2004).

142. A company may apply for accreditation as a whole unit regardless of the number of IRBs or separate departments, but in large corporations, individual companies, plants, or facilities that are functionally separate can apply as individual entities. AAHRPP, Who Is Eligible for Accreditation?, *at* http://www.aahrpp.org/eligibility.htm (last visited Mar. 4, 2004).

143. AAHRPP, Accreditation Step by Step, *at* http://www.aahrpp.org/steps.htm (last visited Mar. 4, 2004). Site observers must be allowed to enter any and all facilities in which participants are observed, treated and interviewed, and must have access to all

ganizations which are accredited must be re-evaluated every three years.[144] In intervening years, AAHRPP requires organizations to submit annual reports, information about significant events that may alter the effectiveness of the organization's Human Rights Protection Program (HRPP),[145] and any reports of government sanctions.[146]

The AAHRPP reviews five domains: the organization seeking the accreditation;[147] the research review unit;[148] the investigator;[149] the sponsor;[150] and the participant.[151] AAHRPP has a detailed set of standards for each domain, and a comprehensive evaluation document which allows monitors to address compliance in each area.[152]

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records. AAHRPP, AAHRPP Accreditation Standards, *at* http://www.aahrpp.org/AAHRPP_Accreditation_Standards.htm (last visited Mar. 4, 2004). Obviously, the need for onsite review makes review of organizations in foreign countries more difficult and more expensive. However, if AAHRPP were even to review the IRBs located in foreign countries — leaving it to the IRBs to review the actual sites of clinical trials — this would be an improvement over current practices, under which foreign IRBs are given free rein.

144. AAHRPP, Accreditation Step by Step, *at* http://www.aahrpp.org/steps.htm (last visited Mar. 4, 2004).

145. Research organizations and sponsors have programs (*see supra* Part II.B) designed to protect human subjects of clinical trials. These are called HRPPs.

146. In annual reports, organizations must disclose problems or deficiencies reported in the last twelve months and how they were resolved, program changes that may influence the HRPP, and results of federal or accreditation reviews of the HRPP. They must also inform AAHRPP, as soon as possible, but preferably within seventy-two hours, of any inquires from governmental oversight bodies that might result in a for-cause investigation and any changes in the HRPP that might affect the ability to conform to AHRPP standards, and must report within twenty-four hours any government sanctions. AAHRPP, Maintaining Your AAHRPP Accreditation, *at* http://www.aahrpp.org/maintain.htm (last visited Mar. 4, 2004).

147. The organization applying for accreditation assumes responsibility for the HRPP. AAHRPP, The 5 Domains of AAHRPP Standards, *at* http://www.aahrpp.org/domains.htm (last visited Aug. 29, 2004).

148. *Id.* The AAHRPP examines the arrangements that the organization has made for an independent review of ethical and scientific aspects of research protocol (generally carried out by an IRB). It requires that IRBs review the scientific merits of a research protocol, weigh the risks and benefits to participants and the benefits to society, and review the research on an on-going basis. In part, IRBs must monitor reports of new information regarding the risks and benefits of the trial, and must ensure that participants' interests are protected on an ongoing basis.

149. *Id.* AAHRPP examines the arrangements the organization has to ensure that those conducting research understand and fulfill their responsibilities.

150. *Id.* AAHRPP also examines the organization's arrangements with those who fund or initiate research and are external to the organization (federal agencies, foundations, and corporations).

151. *Id.* In particular, the AAHRPP looks at the arrangements the organization has made for the needs and concerns of its research participants and their communities.

152. AAHRPP, The AAHRPP Evaluation Instrument, *available at* http://www.aahrpp.

AAHRPP publishes the name (and accreditation status) of those entities that receive full or qualified accreditation, but does not disclose those entities who fail to receive accreditation, or who are in engaged in the accreditation process. Entities on probation, or who have accreditation revoked, are not characterized as such, but are removed from accreditation roles.[153]

2. *The Partnership for Human Research Protection (PHRP)*

The PHRP is a joint venture between the Joint Committee of the Accreditation of Health Care Organizations and the National Committee for Quality Assurance. PHRP takes a slightly different approach to accreditation than AAHRPP. Like AAHRPP, it is designed to protect human subjects of medical experimentation. PHRP's primary focus, however, is whether the Human Rights Protection Program ensures that "avoidable harms are minimized." PHRP also places more emphasis on self-evaluation and does not explicitly assert that it will review either corporations or international entities.[154]

PHRP's review consists of three steps: a web-based self-assessment, a PHRP review of that assessment, and an on-site visit. PHRP emphasizes in particular its "web-based readiness evaluation tool." This tool serves two functions. An organization first uses it to evaluate its own HRPP standards against those of PHRP in order to determine whether or not the organization is ready for PHRP evaluation. Once the organization decides that it has attained PHRP standards, it submits the web-based evaluation, along with supporting documentation, in order for PHRP to begin its review of the organization. This documentary review is followed by on-site visits where "a team of expert surveyors will validate performance against PHRP standards."

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org/tool.htm (last visited Aug. 29, 2004).

153. AAHRPP, Confidentiality, *at* http://www.aahrpp.org/confidentiality.htm (last visited Mar. 4, 2004).

154. According to its website, PHRP will review hospitals, research institutions, government research centers, universities, academic medical centers and IRBs. While this list is not exclusive, there is no reference to review of corporations. In addition, PHRP's website does not address whether it will review international entities. PHRP, PHRP Brochure, *available at* http://www.phrp.org/images/pubs/phrp/PHRPbroch%20.pdf (last visited Aug. 30, 2004).

On its website, PHRP discloses to the public the organization's accreditation status (and the date that accreditation expires, if applicable), along with information such as its name, address, phone number, and email address. PHRP also discloses the organization's scheduled survey dates, applicable standards, and the fee schedule for that particular group.[155] PHRP does not report the initial survey itself. However, if PHRP is conducting a discretionary review to determine whether there has been "a serious breach in compliance with accreditation standards," PHRP will publish the organization's status as "under review."[156] PHRP also makes available to "applicable regulatory agencies" information related to PHRP-identified conditions that "pose[ ] a potential imminent threat" to research participants.[157] PHRP, however, will keep materials relating to the accreditation decision, written survey and staff analysis, the accreditation decision report sent to the institution, or information relating to a process unique to the organization confidential.[158]

B. ACCREDITATION OF PHARMACEUTICAL COMPANIES SPONSORING CLINICAL TRIALS IN DEVELOPING NATIONS

Accreditation could prove highly effective in improving standards in clinical trials in many ways. Institutions at several levels — the sponsor of the trial, the institutional review board, or the medical center in which the trial takes place — could seek accreditation themselves, while others — companies or government agencies — could *require* accreditation of some form for the research they sponsor or regulate. For example, a pharmaceutical company could either seek accreditation for its own research programs, or could refuse to sponsor trials that are not approved by an accredited IRB. Similarly, the FDA could require that all research programs run by a pharmaceutical company be accredited before the drugs resulting from that program receive FDA approval, or could choose only to accept the results of trials which

155. Though PHRP claims that it will publish fee schedules, it has not as of yet made those fees available to the public. *See* PHRP, PHRP Public Information Policy, *at* http://www.phrp.org/ (last visited Aug. 30, 2004).

156. *Id.*

157. *Id.*

158. *Id.*

had been approved by an accredited IRB. Some of the ways in which such accreditation could work are outlined below.

Clinical trials that are planned far in advance of implementation, as opposed to those which take place during a medical emergency, could be reviewed by either local accredited IRBs in the host countries — particularly in those countries which are regularly host to such trials — or by accredited IRBs in the home country.[159] Just as Nike only purchases sneakers from FLA-certified factories, so too could Pfizer could only sponsor trials in accredited research centers or reviewed by accredited IRBs.

In addition, pharmaceutical companies could seek accreditation for themselves. For example, Pfizer could have individual research groups — such as the Trovan group — reviewed by accrediting boards. For now, however, even for clinical trials in the United States, PhRMA has taken the position that voluntary industry efforts are "working well."[160] Though PhRMA promises to "monitor the accreditation efforts," until it embraces accreditation for trials in the United States, it is unlikely to embrace accreditation for trials that are conducted abroad.[161]

The FDA, if convinced, could provide leverage by granting expedited approval to those organizations which are working with an accreditation program. Accreditation would relieve some of the pressure on the FDA to police research groups' protections of human subjects. PHRP, for example, reports information to regulatory agencies when it deems that there is a threat to the health or safety of research participants. Accreditation programs could alert the FDA to problems with clinical trials in developing nations (which, as noted above, the FDA lacks the resources to police itself).

Accreditation that ensures compliance with international human rights standards in clinical trials conducted in developing countries may still be far off. However, the recent adoption of specific standards by the industry (through PhRMA) and by indi-

159. In certain circumstances, accrediting clinical trials in developing nations may be impractical. For example, it would be prohibitively expensive to accredit medical centers which are the site for a single clinical trial or which are set up in an emergency situation. Additionally, in such emergency situations, there may not be a local accredited IRB capable of approving research protocol.

160. Landro, *supra* note 6.

161. *Id.*

vidual companies (such as Pfizer and Bristol Meyers Squibb) indicates that the industry is responding to criticism of its clinical trials procedures. If the media and the public pay more attention to the problems of international clinical trials, then perhaps consumer and investor pressure on the industry will continue to grow. The only workable means of ensuring that American medicine does not provide benefit at the expense of the inhabitants of developing nations is for the FDA, or the industry, to accept accreditation of organizations conducting clinical trials on human subjects.