

SOMEWHERE TO RUN, SOMEWHERE TO HIDE?: INTERNATIONAL REGULATION OF HUMAN SUBJECT EXPERIMENTATION

ADAM H. LAUGHTON*

INTRODUCTION

The pharmaceutical industry is one of the most important players in the field of clinical research on human beings. Increasingly in recent years, “Big Pharma” in the United States and elsewhere has turned to foreign populations to test its new products. The purpose of this note is to examine how existing sources of quasi-legal and ethical regulation address the troublesome issues raised by this increase in international human experimentation. First, the note gives a brief history of human experimentation and its regulation, giving special focus to the events of the twentieth century that have most affected the development of the bioethics movement. Next, it describes and compares several instruments of international regulation of human subject experimentation. Finally, it examines some of the difficult ethical issues associated with international research on human subjects. In this discussion, the greatest amount of attention will be given to clinical trials performed by the pharmaceutical industry. Other types of international research on human subjects exist, but research by the pharmaceutical companies poses its own special regulatory and ethical problems.

I. HISTORY AND BACKGROUND

A. Pre-Nuremberg

Though the Holocaust and the concurrent Nazi experimentation on prisoners and Jews¹ brought unprecedented attention to

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* Adam H. Laughton is a J.D. candidate at Duke University School of Law and an Executive Editor of the *Duke Journal of Comparative and International Law*. He would like to thank his wife Ariel Bybee Laughton for her constant support in all of his academic endeavors.

1. See *infra* Part I.B.

experiments on human subjects, such experimentation and ethical reflection thereon began much earlier. One of the earliest codes of medical ethics was the Hippocratic Oath.² The Hippocratic Oath's focus is on care that directly benefits the patient; however, as in many early documents regarding ethics and human experimentation, that benefit is determined by the doctor and not the patient.³ While the oath does not directly address human research,⁴ the issue of delegating decision-making to physicians arises in later international codes and agreements on human experimentation.

Perhaps as a result of the lack of attention to human subject research, experimentation continued unabated and largely unregulated until the 19th century.⁵ In 1803, Thomas Percival, an English physician, promulgated a code of medical ethics that dealt directly with human experimentation.⁶ Like the Hippocratic Oath, Percival's code is decidedly skewed towards the interests of physicians and experts. There is no mention of consent or other protections of human subjects.⁷ The first American code of ethics dealing with human experimentation was created by William Beaumont in 1833.⁸ The most important aspect of Beaumont's code, in comparison with that of Percival, is that it recognizes the necessity of the subject's voluntary consent and requires that experimentation cease if, at any time, the subject is "distress[ed]" or "dissatisfied."⁹ In 1865, the French physiologist Claude Bernard published his own guidelines governing human experimentation, which precluded any human experimentation that would not be of direct benefit to the patient, no matter its value to science.¹⁰ However, the valuation of that benefit remained in the discretion of the physician.

Ironically, one of the first official regulations of human experimentation came out of the Prussian government in 1900,¹¹

2. See Michael A. Grodin, *Historical Origins of the Nuremberg Code*, in *THE NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION* 121, 123 (George J. Annas & Michael A. Grodin eds., 1992).

3. *Id.* at 123-25.

4. *Id.* at 123.

5. See *id.* at 124 (giving examples of human research involving experimental vaccinations of children and prisoners).

6. *Id.*

7. *Id.* at 125.

8. See *id.*

9. *Id.*

10. *Id.* at 125-26.

11. *Id.* at 127.

which was then part of the German Empire.¹² The Prussian directive expressly prohibited non-therapeutic research either on incompetent individuals (including children) or where the subject had not given “unequivocal[]” consent to the procedure after having it explained to him.¹³ Historical records and contemporary press reports show that these guidelines were largely ignored by German medical researchers throughout the decades between their promulgation and 1931—when new guidelines were introduced.¹⁴ These new guidelines were generated by the Reich Health Council and published by the Reich Minister of the Interior in response to reports of lax ethical standards among German medical researchers.¹⁵ The new standards were among the most comprehensive and protective of the patients’ interests, as compared with other codes of ethics then extant.¹⁶ Experimentation on dying persons was strictly prohibited and research on minors was circumscribed.¹⁷ The Reich Circular required that human research be carried out only after laboratory testing and animal studies were completed.¹⁸ Furthermore, it required informed consent of patients and introduced more extensive protections for “scientific experimentation” (non-therapeutic research) than for “innovative therapy” (therapeutic research).¹⁹ These German regulations are particularly relevant because they were the standards that existed at the time of the Nazi experiments, and against which the Nazi doctors at Nuremberg themselves wished to be judged.²⁰

B. The Nuremberg Doctors Trial

The precipitating crisis of the modern bioethics movement was the extensive and cruel human experimentation performed on

12. See Historical Atlas of Europe, Complete Map of Europe, Year 1900, http://www.euratlas.com/history_europe/europe_map_1900.html (last visited Jan. 25, 2008).

13. Grodin, *supra* note 2, at 127.

14. *Id.* at 128-29 (detailing the following problems: “placing the lives of small children on the same level as those of . . . rats[,] . . . mental and physical torture[,] . . . disgustingly shameful abominations in the name of science run mad[, and] . . . discrimination between the rich and the poor”).

15. *Id.* at 129.

16. *Id.* at 129, 131-32.

17. *Reichsgesundheitsblatt* 11, No. 10, 174-75 (Mar. 1931), reprinted in 31 INT’L DIG. OF HEALTH LEGIS. 408, 408-11 (1980).

18. *Id.* Interestingly, a 1933 law by the Nazis effectively prohibited experimentation on animals but left the guidelines otherwise intact. Grodin, *supra* note 2, at 132.

19. See *Reichsgesundheitsblatt*, *supra* note 17.

20. Grodin, *supra* note 2, at 126.

prisoners of the Nazi regime and the subsequent trial of twenty-three Nazi doctors at Nuremberg, Germany beginning in December 1945. During the Nazi regime, the practice of medicine was perverted from its typical purposes of healing and aiding the sick and suffering and was used instead to promote “ideas and solutions to the racial problems” that the Nazis perceived were a plague on their country.²¹ This shift could represent a compelling explanation of why German medical science moved away from the high ethical and professional standards that it had previously set²² and toward the realm of pseudo-science and torture. The Nazi doctors performed a wide variety of human experiments on prisoners (particularly Jews and gypsies) during the course of the regime, including extended immersion in cold water, extreme exposure to high-altitude conditions, exposure to military biochemical agents, and sterilization.²³ Often, these experiments resulted in death (as they were designed to do).²⁴

At the conclusion of the Nuremberg trial, fifteen of the twenty-three doctor defendants were found guilty, including Karl Brandt, who had been Hitler’s personal physician and Reich Commissioner for Health and Sanitation, one of the highest-ranking positions in the Nazi medical system.²⁵ Seven of these fifteen were sentenced to death by hanging and the rest were sentenced to prison terms of various lengths.²⁶ Alongside the final criminal judgment of the defendants, the Nuremberg judges enumerated ten principles regarding acceptable human experimentation.²⁷ The proximate origin of these principles was the contributions of two key experts for the prosecution, Dr. Leo Alexander and Dr. Andrew Ivy, who drew on historical sources such as the Hippocratic Oath.²⁸ Dr. Ivy testified at trial and Dr. Alexander had drawn up a memorandum for the judges, each focusing on ethical principles related to human experimentation.²⁹ Today, the Nuremberg Code is probably “the

21. Joel Levi, *Medicine, the Holocaust, and the Doctors’ Trial*, in *BIOETHICAL AND ETHICAL ISSUES SURROUNDING THE TRIALS AND CODE OF NUREMBERG: NUREMBERG REVISITED* 111, 114 (Jacques J. Rozenberg ed., 2003).

22. *See supra* Part I.A.

23. HORST H. FREYHOFER, *THE NUREMBERG MEDICAL TRIAL: THE HOLOCAUST AND THE ORIGIN OF THE NURSEMBERG MEDICAL CODE 26-37* (Peter Lang ed., 2004).

24. *Id.*

25. Levi, *supra* note 21, at 116, 124.

26. *Id.* at 124.

27. Grodin, *supra* note 2, at 121.

28. *Id.* at 134.

29. *Id.*

most accepted” and “the most cited” medical code of ethics.³⁰ More will be said about the content of the Nuremberg Code in Part II.A of this Note.

C. Other Human Experiments Outside of Germany in the Twentieth Century

It is important to remember that during World War II, and even after, unethical human experiments were not being carried out solely by the Nazis. Other countries, including Japan and the United States, carried out similarly brutal and unethical experimentation. The Japanese used U.S. prisoners of war (POWs) in their biological warfare experiments in China.³¹ Other weapons, such as flamethrowers and grenades, were tested on human subjects, including Allied POWs and Chinese living in the areas surrounding concentration camps.³² Finally, a horrifying array of live human vivisections, amputations, and experiments involving exposure to various extreme conditions (pressure, centrifugal force, deprivation, hunger and thirst) were performed by the Japanese on human subjects.³³ Despite the gruesome nature of their crimes, often similar to those for which the Nazi doctors were punished, many Japanese doctors were offered immunity from prosecution by the United States in exchange for disclosing the results of their experiments.³⁴

Perhaps most troubling from the American point of view is the behavior of American scientists after the war with regard to human experimentation. One example was a series of human radiation experiments carried out with the support of various bodies of the federal government throughout the first thirty years of the Cold War (roughly 1940s-1970s).³⁵ Over seven hundred American patients, including terminally ill hospital patients, were used as part of thirty-

30. Levi, *supra* note 21, at 116.

31. George J. Annas, *The Nuremberg Code in U.S. Courts: Ethics versus Expediency*, in *THE NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION*, *supra* note 2, at 201, 202.

32. See Christopher Hudson, *Doctors of Depravity*, *THE DAILY MAIL* (UK), Mar. 2, 2007, http://www.dailymail.co.uk/pages/live/articles/news/news.html?in_article_id=439776.

33. See *id.*; Shane Green, *The Asian Auschwitz of Unit 731*, *THE AGE*, Aug. 29, 2002, <http://www.theage.com.au/articles/2002/08/28/1030508070534.html>.

34. Annas, *supra* note 31, at 202; see also Hudson, *supra* note 32.

35. George J. Annas, *Questing for Grails: Duplicity, Betrayal, and Self-Deception in Postmodern Medical Research*, in *HEALTH AND HUMAN RIGHTS* 312, 316 (Jonathan M. Mann et al. eds., 1999).

one experiments.³⁶ Later reports indicated that the patients were given no information about the purpose of the experiments, and consent was not part of the research protocol.³⁷ In one dramatic example, a man had plutonium injected into his leg, which was then amputated for study. The man was subsequently unable to work or support himself.³⁸ A federal judge, in a lawsuit by the families of the subjects (most now dead), stated that the patients had allegedly been treated “as though they were laboratory animals.”³⁹

Another infamous example of American human experimentation during the Cold War concerns the Central Intelligence Agency’s MKULTRA experiments.⁴⁰ In its MKULTRA research and related experiments, the CIA was interested in the effects of drugs, hypnosis, and radiation for purposes of mind control and interrogation.⁴¹ One of the arms of the MKULTRA experiments involved administering LSD to “volunteers” who were unaware of the nature of the experiment to which they would be subjected; other truly non-volunteer subjects were randomly slipped LSD in bars in New York City and San Francisco.⁴² These experiments resulted in the accidental death of at least one subject.⁴³

Easily the most well-known of any human experiment carried on by the United States is the Tuskegee Syphilis Study. Beginning in 1932, the United States Public Health Service initiated an experiment with 600 black males in Tuskegee, Alabama, the purpose of which was to study the natural history and progression of syphilis.⁴⁴ When the study began, over half the men were already infected with the disease.⁴⁵ In exchange for their participation in the study, the subjects

36. *Id.* at 316-17.

37. *Id.* at 317.

38. *Id.*

39. *Id.* at 319. This much was admitted by researchers, who claimed that “[o]f the common laboratory animals, man appears to correspond most closely to the rat in regard to intravenous tolerance to uranium.” *Id.* at 317.

40. MKULTRA is the most well-known of a series of CIA experiments that carry similar designations. All of these involved testing the use of drugs or biochemical compounds on non-volunteers. ANDREW GOLISZEK, *IN THE NAME OF SCIENCE: A HISTORY OF SECRET PROGRAMS, MEDICAL RESEARCH, AND HUMAN EXPERIMENTATION* 151, 153-55 (2003).

41. *Id.*

42. *Id.* at 158, 160.

43. *Id.* at 159-60. For detailed information about the history of CIA human experimentation, see *id.* ch. 5.

44. Ctrs. for Disease Control and Prevention, U.S. Dep’t of Health and Human Servs., *The Tuskegee Timeline*, <http://www.cdc.gov/nchstp/od/tuskegee/time.htm> (last visited Jan. 9, 2008).

45. *Id.*

received free food and medical care.⁴⁶ However, the true nature of the experiment was never explained to any of the subjects, and even when an effective treatment to cure syphilis was discovered, it was not offered to any of the study subjects.⁴⁷

The Tuskegee study went on for an amazing forty years before it was discovered and revealed by the press.⁴⁸ The increased scrutiny and criticism of the study by the press and government advisory panels led to its immediate termination.⁴⁹ Some compensation was provided to the victims of the study in 1973, but it was not until 1997 that President Bill Clinton apologized for the injustice that had been done to the experiment's subjects.⁵⁰ The revelation of the Tuskegee experiments resulted in the passage of the National Research Act in 1974,⁵¹ which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.⁵² In 1979, the Commission published the Belmont Report which identified "basic ethical principles" and applications of those principles that were relevant to human subject research.⁵³ The recommendations of the Belmont Report were adopted by the Department of Health and Human Services and many other federal agencies and incorporated into their regulations.⁵⁴ These recommendations evolved into what is currently known as the "Common Rule" for human research protection.⁵⁵

D. The AZT 076 Clinical Trials in Africa

The next crisis in the history of international human subject research revolved around the most significant global health crisis of the late 20th century—HIV/AIDS. In 1997, several of the specific

46. *Id.*

47. *Id.*

48. *Id.*

49. *Id.*

50. *Id.*

51. National Research Services Act of 1974, Pub. L. 93-348, 88 Stat. 342; Ctrs. for Disease Control and Prevention, U.S. Dep't of Health and Human Servs., U.S. Public Health Service Syphilis Study at Tuskegee, <http://www.cdc.gov/tuskegee/after.htm> (last visited Jan. 14, 2008).

52. Office of Human Subjects Research, Nat'l Insts. of Health, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, Apr. 18, 1979, <http://www.nihtraining.com/ohsr/site/guidelines/belmont.html>.

53. *Id.*

54. See Office for Human Research Protections, U.S. Dep't of Health and Human Servs., Belmont Report, <http://www.hhs.gov/ohrp/belmontArchive.html> (last visited Jan. 14, 2008).

55. *Id.*; see 45 C.F.R. § 46 (2006).

ethical issues surrounding international drug trials became part of a passionate dispute about AIDS-related research. The National Institutes of Health had funded a trial of a new protocol of AZT, an important retroviral drug used in AIDS therapy, in several African, Asian, and Caribbean countries.⁵⁶ An earlier test of AZT Protocol 076 had demonstrated a two-thirds reduction in mother-to-child HIV transmission.⁵⁷ Because of the high cost of AZT and that fact that Protocol 076 was an intensive treatment regimen, the prospects for providing the drug to HIV patients in impoverished countries were bleak.⁵⁸ Therefore, the new protocol involved a shortened regimen of AZT which was tested against a placebo.⁵⁹ The trial researchers claimed that they were looking for a more cost-effective, and therefore more accessible, manner of providing treatment.⁶⁰

Several researchers argued that use of a placebo in these trials, given that a proven therapy was known, was unethical.⁶¹ The placebo arm of the trial, under the circumstances, would have been legally barred in the United States.⁶² The trial's supporters were charged with applying a double standard and exploiting trial participants because of lower standards abroad.⁶³ Opponents also claimed that even the shortened AZT regimen would have been too expensive in certain trial sites where the average annual health expenditure was only about ten dollars.⁶⁴ Trial supporters fired back, claiming that the use of a placebo-controlled trial was essential in rendering a faster, more useful and scientifically reliable answer about the efficacy of the shortened regimen, and would, in the end, benefit the countries in which the trials were being performed.⁶⁵ Trial researchers responded to charges of exploitation with claims that their opponents were "ethical imperialists," seeking to impose Western standards that

56. AURORA PLOMER, *THE LAW AND ETHICS OF MEDICAL RESEARCH: INTERNATIONAL BIOETHICS AND HUMAN RIGHTS* 114 (2005).

57. *Id.*

58. *Id.* at 115. The cost per patient at the time was approximately \$800. *Id.*

59. *Id.* at 114.

60. *See id.* at 115.

61. Peter Lurie & Sid M. Wolfe, *Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries*, 337 *NEW ENG. J. MED.* 853, 853 (1997). It is also important to note that in the earlier test of Protocol 076, once the dramatic efficacy of the treatment was discovered, the placebo arm of the test was shut down immediately. *Id.*

62. PLOMER, *supra* note 56, at 114.

63. Lurie & Wolfe, *supra* note 61, at 855.

64. PLOMER, *supra* note 56, at 115.

65. *Id.*

would prevent the needs of developing world populations from being met.⁶⁶

In the end, the short regimen of AZT had rates of success similar to Protocol 076.⁶⁷ Future clinical trials would compare the results of this short-course AZT regimen against those of even less intensive and costly regimens of competing retrovirals, such as nevirapine, which proved to be even more effective in preventing mother-to-child HIV transmission.⁶⁸ This episode illustrates several of the enduring and relevant debates surrounding pharmaceutical trials overseas.

E. The Contemporary Background of International Clinical Trials

The pharmaceutical industry has legitimately earned its common moniker “Big Pharma.” It has been the most consistently profitable industry since World War II.⁶⁹ In 2005, global pharmaceutical spending exceeded \$600 billion.⁷⁰ This represents a growth rate of seven percent worldwide, but emerging markets in Asia, Europe and Latin America grew even faster.⁷¹ However, the development pipeline for new pharmaceutical products is a lengthy and costly one. The typical drug costs about \$802 million over the course of its research and development, which lasts ten to fifteen years.⁷²

The most difficult hurdle for new drugs to overcome is Food and Drug Administration (FDA) approval, the *sine qua non* of drug marketability in the United States. The FDA approval process, which is overseen by the FDA’s Center for Drug Evaluation and Research (CDER),⁷³ consists of a series of four phases of clinical trials.⁷⁴ These

66. *Id.* at 116.

67. SONIA SHAH, *THE BODY HUNTERS* 97 (2006).

68. *Id.* at 98.

69. Annas, *supra* note 35, at 324.

70. Press Release, IMS Health, IMS Health Reps. Global Pharm. Mkt. Grew 7 Percent in 2005, to \$602 Billion (Mar. 21, 2006), *available at* http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_77491316,00.html.

71. *Id.*

72. PHARMA, *PHARM. INDUS. PROFILE 2007*, at 5-6, *available at* <http://www.phrma.org/files/Profile%202007.pdf>.

73. *See* Ctr. for Drug Evaluation and Research, U.S. Food and Drug Admin., Frequently Asked Questions, <http://www.fda.gov/cder/about/faq/default.htm> [hereinafter CDER FAQ] (last visited Jan. 14, 2008).

74. Barr Pharmaceuticals, Proprietary Product FDA Approval Process, <http://www.barrlabs.com/proprietary/approval.php> (last visited Jan. 14, 2008); *see also* CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMIN., *CDER HANDBOOK 19*, *available at* <http://www.fda.gov/cder/handbook/handbook.pdf> (last visited Jan. 14, 2008).

trials test a new drug's safety and efficacy.⁷⁵ The approval process also involves institutional review by the FDA, and meetings between the new drug's sponsor and the CDER.⁷⁶ Each of the first three phases of a clinical trial require progressively more test subjects, peaking at around 3,000 for a Phase III trial.⁷⁷ Because not all patients who apply for a place in a clinical trial will be eligible, and many eligible subjects may not show up for their scheduled check-ups or follow the prescribed protocol, new drug sponsors may have to find many more willing subjects than the number required for the trial to get off the ground.⁷⁸

A problem facing pharmaceutical companies who need a trial with several thousand willing participants is that Americans are increasingly hesitant to participate in these experiments.⁷⁹ The lack of clinical trial volunteers has caused a back-up in the "pipeline" of developing drugs.⁸⁰ Though both the cost and the number of new drug trials have increased in the past few years, the annual output of new FDA-approved drugs has remained steady.⁸¹ The immediate effect of this trend has been to transfer the task of finding and carrying out new trials from academic medical centers, which the pharmaceutical industry saw as too slow to review and carry out the trials, to contract research organizations (CROs).⁸² CROs are independent contractors who perform the tests and compile and submit the results to the FDA on behalf of the drug companies.⁸³

CROs are more aggressive and faster in finding patients and carrying out the trials and were the main proponents of moving more

75. Barr Pharmaceuticals, *supra* note 74.

76. *Id.*

77. ClinicalTrials.gov, Understanding Clinical Trials, <http://clinicaltrials.gov/ct2/info/understand> (last visited Jan. 14, 2008). Phase IV trials are post-marketing trials that test long-term effectiveness and safety. CenterWatch, Background Information on Clinical Research, <http://www.centerwatch.com/patient/backgrnd.html> (last visited Jan. 14, 2008).

78. SHAH, *supra* note 67, at 3.

79. *See id.* at 4-5 (noting that less than one in twenty Americans is willing to take part in clinical trials and less than four percent of cancer patients would participate in a new cancer drug trial). Until the ethical reforms of the 1970s outlawed it, the U.S. prison population presented a "captive audience" of subjects for new drug trials. *Id.* at 6.

80. *Id.* at 3.

81. *Id.* at 5.

82. *Id.* at 6.

83. 21 C.F.R. § 312.3(b) (2007) ("Contract research organization means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.").

clinical trials overseas.⁸⁴ The role of CROs has plausibly led many pharmaceutical companies, including some industry giants like GlaxoSmithKline and Merck, to conduct between thirty and fifty percent of their clinical trials overseas.⁸⁵ The number of clinical investigators overseas is growing too—up eight percent between 2001 and 2003, with a corresponding eleven percent decrease in the number of U.S. researchers.⁸⁶ New trials are generally moving toward more impoverished countries with larger “sick” populations—including Russia, India, and countries in Eastern Europe and Latin America.⁸⁷

The shift of clinical trials to sites abroad has important implications for both countries hosting trials and those whose companies are sponsoring the research. Overseas clinical trials may be cheaper than domestic trials and may also enable new drugs to reach the market faster, resulting in greater profits for the pharmaceutical companies. The rapid approval and introduction of new drugs will likely result in increased health (or increased sickness if the testing is carried out poorly) for the populations to whom the drugs are marketed, which is not always the population on which the drug was originally tested. For the countries that host the clinical trials, their health systems may receive valuable infusions of capital by pharmaceutical companies who are anxious to carry out trials using local populations and researchers. The new drug and its post-trial availability (or lack thereof) will affect health outcomes for the test subjects in the host country as well. For these reasons and others, it is important now to ask what legal or ethical guidelines govern the conduct of clinical trials abroad and whether they are effective in regulating unethical or exploitative behavior by researchers.

II. DESCRIPTION AND COMPARISON OF MAJOR INTERNATIONAL AGREEMENTS OR CODES OF ETHICS REGARDING HUMAN EXPERIMENTATION

There are numerous important international documents that touch on human subject experimentation, and new instruments seem

84. See SHAH, *supra* note 67, at 6-7.

85. *Id.* at xi.

86. *Id.*

87. *Id.* at 7. Shah also notes that many of the conditions that led these countries to have such impoverished and sick populations were the result of the interactions, such as colonialism and globalization, with Western countries that are now sending their pharmaceutical products across the world for testing. *Id.* at 15.

to appear each year. Not all of them can be mentioned here, nor can any one of them be examined in full detail.⁸⁸ Instead, this Note looks at two of the most influential international codes of ethics and two others which represent new approaches by those who seek to protect human subjects from unethical research practices.

A. The Nuremberg Code

The importance of the Nuremberg Code (Code) as a point of departure for the bioethics and broader human rights movements can hardly be overstated. The Code is recognized as “an authoritative statement of the fundamental rights of research subjects in all nations.”⁸⁹ Further, the Code has influenced the development of subsequent human rights documents that go beyond the scope of human subject experimentation.⁹⁰

Aside from the Code’s significance and continued influence as a symbolic beginning to the regulation of human subject research, its content offers several points of comparison that are relevant to an analysis of subsequent bioethics documents. The Code itself consists of ten principles, stated in simple and direct terms. The first in order and importance says simply, “[t]he voluntary consent of the human subject is absolutely essential.”⁹¹ The paragraph which follows explains that the consent must be given by a person “so situated as to be able to exercise free power of choice,” free from “any element” of coercion and based on prior information given to the subject about the nature of the experiment, its purposes, and the risks involved.⁹² The principle of informed consent is the Code’s “most important

88. See generally Sev S. Fluss, *The Evolution of Research Ethics: The Current International Configuration*, 32 J.L. MED. & ETHICS 596 (2004) (containing a more extensive list of ethical guidance instruments).

89. Nicholas A. Christakis & Robert J. Levine, *Multinational Research*, in 3 ENCYC. OF BIOETHICS 1780, 1780 (Warren Thomas Reich ed., 1995).

90. The Nuremberg Code provisions have found expression in prohibitions on the use of wounded soldiers, prisoners of war, and civilians of an occupied state in non-therapeutic experimentation as part of the 1949 Geneva Conventions I (art. 12), II (art. 12), III (art. 13), and IV (art. 32). Sharon Perley et al., *The Nuremberg Code: An International Overview*, in THE NAZI DOCTORS AND THE NUREMBERG CODE, supra note 2, at 149, 153-54. The Code also influenced the wording of the International Covenant on Civil and Political Rights, which states, “In particular, no one shall be subjected without his free consent to medical or scientific experimentation.” International Covenant on Civil and Political Rights art. 7, Dec. 16, 1966, 999 U.N.T.S. 171. The use of the language of “free consent” is consistent with the language of the Code. Perley, supra, at 153.

91. Nuremberg Code, princ. I (1947), reprinted in 313 BRIT. MED. J. 1448, 1448 (1996).

92. *Id.*

contribution” and has enjoyed wide acceptance in the research community.⁹³ None of the other nine provisions of the Code derogates from the researcher’s “personal duty” to procure and protect the subject’s informed consent. The rigidity of the Code’s requirements, and therefore the limits which it placed on research, is one reason why the medical research community has tried to “improve” upon it in other instruments.⁹⁴

In addition, the Code demands that research be performed “as to yield fruitful results for the good of society, unprocurable by other methods or means of study”⁹⁵ In spite of the recognition that research ought to produce some benefit, the Code mentions nothing about the distribution of that benefit. Moreover, the Code is entirely devoted to experiments performed on healthy patients. No alternatives are mentioned for research combined with treatment, or therapeutic research.

Though the Code is a legal document, produced as part of an international criminal trial, it has no legal force.⁹⁶ A related criticism of the Code is that the duty to follow its precepts is placed entirely on the researcher, who presumably is interested in the success of the experiment.⁹⁷ Even as a document written by judges, it is to be entirely self-enforced. The Code establishes no outside compliance review or method of sanctioning non-compliance. Of this particular limitation, perhaps we should be more forgiving. Though the Nuremberg judges intended to set forth ethical guidelines of enduring significance, it is important to remember that the Code was written in response to a discrete set of historical events, namely the Holocaust and the crimes of the Nazi doctors. The judges were responding to the specific crimes and evidence before them. The Nuremberg Code as a whole is a limited and simple document. Future instruments have added detail and complexity to the principles announced first at Nuremberg.

93. Perley, *supra* note 90, at 155.

94. See *infra* Part II.B (discussing the Declaration of Helsinki), Part II.C (discussing the Council of Europe’s Convention on Human Rights and Biomedicine), Part II.D (discussing the Universal Declaration on Bioethics and Human Rights).

95. Nuremberg Code, *supra* note 91, princ. II.

96. See Perley, *supra* 90, at 160.

97. See Nuremberg Code, *supra* note 91, princs. I, X (assigning to the researcher both the responsibility of obtaining informed consent and of determining when the experiment should be terminated).

The Code's lack of legal force can be observed in the way it has interacted with the U.S. legal system. On the legislative and administrative side, federal regulations depart from the spirit of the Code by introducing the responsibility of the research institution and the authority of institutional review boards (IRBs) in lieu of the Code's emphasis on the researcher's authority.⁹⁸ In U.S. courts, no injured subject has ever been awarded damages, and no researcher has ever been punished based purely on violations of the Nuremberg Code.⁹⁹ The Code has been mentioned far more often as an authoritative source in dissent.¹⁰⁰ Perhaps the apex of the Code's use in U.S. courts was its extensive citation in the dissenting opinions in *United States v. Stanley*, which involved the CIA's MKULTRA experiments.¹⁰¹ The 5-4 majority denied Mr. Stanley, a soldier in the U.S. Army, any compensation for his injuries, but Justice Brennan (joined by Justices Marshall and Stevens) and Justice O'Connor would have used the standards of the Nuremberg Code to provide him with a right to damages.¹⁰²

B. The Declaration of Helsinki

Because of the Nuremberg Code's limitations and perceived flaws, medical researchers soon acted to create their own set of ethical standards. In 1964, the World Medical Association (WMA) issued the Declaration of Helsinki (Declaration), which soon became the definitive statement of medical ethics regarding research.¹⁰³ The

98. Leonard H. Glantz, *The Influence of the Nuremberg Code on U.S. Statutes and Regulations*, in *THE NAZI DOCTORS AND THE NUREMBERG CODE*, *supra* note 2, at 183, 187-88. The Nuremberg Code also has had great influence on the ethical guidelines promulgated by the National Institutes of Health. *Id.* at 186. However, this is of little concern to pharmaceutical companies, whose principal concern is FDA approval.

99. Annas, *supra* note 31, at 201.

100. *Id.* (also noting the irony that the Code has such little legal force even in the United States, the country whose citizens, judges, and procedures produced the Code in the first place). In one lower court case, the Nuremberg Code was cited as setting the standard of the required disclosure of risks by the researcher to the subject. *Whitlock v. Duke Univ.*, 637 F.Supp. 1463, 1470-71 (M.D.N.C. 1986).

101. *United States v. Stanley*, 483 U.S. 669, 671-72 (1987).

102. *Id.* at 687, 690-91, 710.

103. See PLOMER, *supra* note 56, at 2. The World Medical Association was organized in 1947 as a representative body for physicians. *Id.* The WMA is comprised of national physician groups such as the American Medical Association (AMA) in the United States. World Medical Ass'n - List of Members, <http://www.wma.net/e/members/list.htm> (follow "United States" hyperlink) (last visited Jan. 15, 2008).

Declaration has been revised five times since 1964 and has had two notes of clarification added.¹⁰⁴

As originally formulated, the Declaration placed less emphasis on informed consent than the Nuremberg Code. From Nuremberg's characterization of voluntary consent as "absolutely essential,"¹⁰⁵ the original Declaration reads, "*If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation.*"¹⁰⁶ The Declaration also allows consent to be given by a proxy of the subject, in the case of legal or physical incapacity, something which the Nuremberg Code would not allow.¹⁰⁷ In later versions of the Declaration, the sections on informed consent were strengthened, calling for "freely-given informed consent" either written or "formally documented and witnessed."¹⁰⁸

One of the Declaration's most significant contributions to the field of medical research ethics is the introduction of independent committee review of research protocols.¹⁰⁹ According to the Declaration, the independent committee, known in U.S. regulations as an institutional review board (IRB), "should be in conformity with the laws and regulations of the country in which the research experiment is performed."¹¹⁰ The use of foreign IRBs and the problems associated with them will be addressed in Part IV.

As has been noted by ethicists, the Declaration of Helsinki is more permissive and paternalistic than the Nuremberg Code.¹¹¹ In

104. PLOMER, *supra* note 56, at 3; World Med. Ass'n [WMA], Declaration of Helsinki, WMA Policy (Sept. 10, 2004), available at <http://www.wma.net/e/policy/pdf/17c.pdf> [hereinafter Declaration of Helsinki]. The revisions occurred in 1975, 1983, 1989, 1996, and 2000 with the notes of clarification added in 2002 and 2004. Declaration of Helsinki, *supra*.

105. Nuremberg Code, *supra* note 91, princ. I.

106. WMA, Declaration of Helsinki, para. II(1) (June 1964), reprinted in 91 Can. Med. Ass'n J. 619, 619 (1964) (emphasis added), available at <http://www.pubmedcentral.nih.gov/picrender.fcgi?tool=pmcentrez&artid=1927433&blobtype=pdf>. The Declaration also places the provision on informed consent much later than the Nuremberg Code. See *id.*

107. *Id.* para. II(1).

108. Declaration of Helsinki, *supra* note 104, para. 22. Though the provision on informed consent is moved into the section entitled, "Basic Principles for all Medical Research," it still appears in the latter half of the document. See *id.* The newest version of the Declaration still provides for proxy consent, but greater protections of vulnerable or incapacitated persons are provided in those sections. *Id.* paras. 24-26.

109. R.V. Carlson et al., *The revision of the Declaration of Helsinki: Past, Present, and Future*, 57 BRIT. J. CLINICAL PHARMACOLOGY 695, 697 (2004).

110. Declaration of Helsinki, *supra* note 104, para. 13.

111. Annas, *supra* note 35, at 315.

part, this reflects the instruments' different backgrounds. The Nuremberg Code is primarily concerned with human rights, having been drafted by judges in one of the first human rights tribunals.¹¹² The Declaration, on the other hand, was created by doctors for doctors.¹¹³ The increased flexibility was intentional on the part of its drafters who represented the physicians' interests and who felt that the Nuremberg Code was too rigid and legalistic.¹¹⁴

The Declaration was signed by the United States in 1975¹¹⁵ and was incorporated by the FDA into their regulations for overseas clinical research that same year.¹¹⁶ In spite of having been adopted into FDA regulations, the Declaration is a general statement of ethics, not a collection of legally binding principles.¹¹⁷ Neither the WMA, nor the Declaration itself, have established procedures for enforcement or penalties for violators.¹¹⁸ Moreover, the United States has refused to sign on to the latest revision of the Declaration, because of the WMA's insistence that research subjects should have access to the best current treatment rather than the best treatment which would otherwise be available to them.¹¹⁹ This change would have made it more difficult or impossible to perform placebo trials with new drugs if an existing remedy for the same problem already existed.¹²⁰

Where plaintiffs have brought claims against pharmaceutical companies for violations of the Declaration, the results have not been encouraging. For example in *Abdullahi v. Pfizer* Nigerian nationals sued Pfizer, an American pharmaceutical company, under the Alien Tort Claims Act (ATCA), 28 U.S.C. § 1350 (2006).¹²¹ Their claim was based on a drug trial of a new antibiotic, Trovan, which resulted in

112. See *supra* Part II.A.

113. Annas, *supra* note 35, at 315; Perley, *supra* note 90, at 157.

114. See Annas, *supra* note 35, at 315 (suggesting that the Declaration of Helsinki is different from the Nuremberg Code in two relevant ways, namely that the Declaration gives recommendations and that it is more lenient).

115. SHAH, *supra* note 67, at 75.

116. *Id.* at 133. Each time that the Declaration was updated between 1975 and 1996, the regulations were also updated to mirror those changes. *Id.*

117. See Perley, *supra* note 90, at 160 ("Although they are highly influential, neither the Nuremberg Code nor the Declaration of Helsinki has any legally binding authority.").

118. PLOMER, *supra* note 56, at 7.

119. See SHAH, *supra* note 67, at 132-35.

120. See *id.*

121. *Abdullahi v. Pfizer*, No. 01 Civ. 8118, 2002 WL 31082956, at *1 (S.D.N.Y. Sept. 17, 2002), *vacated*, 77 Fed. Appx. 48 (2d Cir. 2003) (vacating the district court's order to dismiss on grounds of *forum non conveniens* and remanding).

the death or serious injury of at least eleven children.¹²² Under the ATCA, plaintiffs must allege violations of the “law of nations” which is comprised of norms which are “specific, universal, and obligatory.”¹²³ The court allowed the Declaration, as well as the Nuremberg Code and other instruments, to be introduced as evidence of principles of customary international law, but eventually found that they were not sufficiently universal to establish a claim under the ATCA.¹²⁴

In addition to the basic principles announced in the Declaration, another international group, the Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO), has published its *International Ethical Guidelines for Biomedical Research Involving Human Subjects*.¹²⁵ The CIOMS Guidelines give more detailed and specific practical guidance concerning the principles found in the Declaration. For example, Guideline 5 sets forth a list of twenty-six items of information that a research subject must be provided before their subsequent consent can be considered informed.¹²⁶ The frequent approving references to the Declaration throughout the Guidelines is evidence that CIOMS believes that the Declaration’s principles are the proper ones.¹²⁷

C. Council of Europe’s Convention on Human Rights and Biomedicine

Next, we turn to a recent European approach to the regulation of clinical trials—the Council of Europe’s Convention on Human Rights

122. *Id.* at *1-2.

123. *Alvarez-Machain v. United States*, 266 F.3d 1045, 1050 (9th Cir. 2001).

124. *See Abdullahi*, 2002 WL 31082956, at *4-6. Civil and criminal lawsuits related to the Trovan study and brought by Nigerian government officials continue in Nigerian courts. *See* Jacob Goldstein, *Nigerian Judge Orders Arrest of Pfizer Officials*, WALL ST. J. HEALTH BLOG, Dec. 26, 2007, <http://blogs.wsj.com/health/2007/12/26/nigerian-judge-orders-arrest-of-pfizer-officials>; Joe Stephens, *Pfizer Faces Criminal Charges in Nigeria*, WASH. POST, May 30, 2007, at A10; Joe Stephens, *Panel Faults Pfizer in ‘96 Clinical Trial in Nigeria*, WASH. POST, May 7, 2006, at A01.

125. COUNCIL FOR INT’L ORG. OF MED. SCI., INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (2002) [hereinafter CIOMS GUIDELINES].

126. *Id.* Guideline 5.

127. *See, e.g., id.* Guideline 13 (Commentary) (noting that the Guideline is “compatible” with the Declaration of Helsinki).

and Biomedicine (CHRB).¹²⁸ The most obvious distinction between the CHRB and the other instruments above is that the CHRB is applicable only in Europe and only to those nations that are members of the Council of Europe.¹²⁹ Currently, the CHRB has been signed by thirty-four of the Council of Europe member nations, but only twenty-one of the signing members, excluding important European powers such as France and Italy, have ratified it.¹³⁰ In addition, Germany, Russian and the United Kingdom are among the nations that have not signed the CHRB.¹³¹

The CHRB is a general human rights instrument concerning not only biomedical research, but also privacy, human genome rights, and the transplantation and trafficking of organs.¹³² The most relevant sections for the purposes of this note are Chapter V on scientific research¹³³ and the Additional Protocol on biomedical research, added in January 2005.¹³⁴ The Chapter V provisions are short and are primarily directed to problems of obtaining consent in the context of research.¹³⁵

The most useful details of the CHRB are added by the Additional Protocol. The Additional Protocol provides for scientific and ethical review by independent committees.¹³⁶ Committee examination is required in “each State in which any research activity is to take place.”¹³⁷ Depending on the scope of the term “research activity,” which remains undefined in both the CHRB and the

128. Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, Apr. 4, 1997, Europ. T.S. No. 164 [hereinafter CHRB].

129. The Council of Europe is often confused with the European Union, but the two are distinct. The Council of Europe is composed of forty-six nations, more than the EU and including important countries not part of the EU such as Russia, Switzerland, and the former Yugoslav republics. Compare The Council of Europe's Member States, http://www.coe.int/T/E/Com/About_Coe/Member_states (last visited Jan. 17, 2008) with Member States of the EU, http://europa.eu/abc/european_countries/index_en.htm (last visited Jan. 17, 2008).

130. See Convention on Human Rights and Biomedicine Chart of Signatures and Ratifications, <http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=164&CM=&DF=&CL=ENG> (last visited Jan. 17, 2008).

131. See *id.*

132. CHRB, *supra* note 128, chs. III, IV, VI.

133. *Id.* ch. V.

134. Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, Jan. 25, 2005, Europ. T.S. No. 195 [hereinafter Additional Protocol].

135. CHRB, *supra* note 128, ch. V.

136. Additional Protocol, *supra* note 134, arts. 7, 9-12.

137. *Id.* art. 9(1).

Additional Protocol (as well as their respective Explanatory Reports), this may include review in the country of origin.¹³⁸ Another important provision added by the Additional Protocol says that research carried out by “[s]ponsors or researchers within the jurisdiction of a Party to this Protocol” that takes place “in a State not party to this Protocol” must comply with the standards of the Protocol if they differ from those in that non-party State.¹³⁹ The drafters of the Additional Protocol were aware of the growing number of research projects being carried out abroad and the possibility of having different standards in different nations.¹⁴⁰ Thus, these more stringent protections are of little value if ethics committee approval in the home country is not required or is weak and ineffective.

A separate section, Chapter II, of the CHRB is devoted entirely to consent, but not solely in the research context.¹⁴¹ Because of its placement separate from the chapter devoted to research ethics, one can deduce that consent is an important and overarching concern for the drafters. An Explanatory Report promulgated with the CHRB makes clear that this formulation of informed consent is meant to restrain physician paternalism¹⁴² and that the information given to the patient must be transmitted in a way that is tailored to the specific person to whom it is communicated such that they can understand the information and weigh the costs and benefits of the procedure.¹⁴³ In the research context, consent must be “express[], specific[], and . . . documented.”¹⁴⁴ Research on persons unable to give consent for themselves is severely restricted.¹⁴⁵ For example, it may not be done if “research of comparative effectiveness” could be “carried out on individuals capable of giving consent” instead.¹⁴⁶ Research is further

138. See *Explanatory Report*, Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, Jan. 25, 2005, Europ. T.S. No. 195, para. 38 (explaining that this would include ethics review in a State where participants are recruited even if the research is physically carried out in another place) [hereinafter *Explanatory Report*].

139. Additional Protocol, *supra* note 134, art. 29 (apparently allowing higher standards in a host country to take precedence over the Protocol, but the Protocol must set the floor).

140. See *Explanatory Report*, *supra* note 138, para. 137.

141. CHRB, *supra* note 128, ch. II.

142. *Explanatory Report*, Convention on Human Rights and Biomedicine, Apr. 4, 1997, Europ. T.S. No. 164, para. 34 [hereinafter *Explanatory Report #2*].

143. *Id.* para. 36.

144. CHRB, *supra* note 132, art. 16(v).

145. *Id.* art. 6(2)-(4) (explaining that as in the Declaration of Helsinki, proxy consent may be given by an authorized legal representative of the patient).

146. *Id.* art. 17(1)(iii).

restricted to instances in which the protocol will produce a direct benefit to the patient, and if not, the research must have the purpose of furthering research that will ultimately produce a benefit to that patient or similarly afflicted individuals and present “minimal risk and minimal burden.”¹⁴⁷

The usefulness of the CHRБ as a device to regulate unethical research is substantially weakened by the lack of an individual’s right to petition the European Court of Human Rights under the CHRБ provisions.¹⁴⁸ The court is authorized to give only an advisory opinion on interpreting the CHRБ.¹⁴⁹ Any enforcement of CHRБ rights is left to the individual states’ courts.¹⁵⁰ However, the rights contained in the CHRБ can be asserted in the European Court of Human Rights if, instead of bringing an action directly under the CHRБ, plaintiffs find a CHRБ right that fits under one of the protections of the European Convention on Human Rights (ECHR), over which that court does have jurisdiction.¹⁵¹ The Explanatory Report to the Convention expressly recognizes the possibility that principles of the CHRБ can be introduced as evidence of the scope of protection offered by the ECHR.¹⁵²

D. Universal Declaration on Bioethics and Human Rights

Of the instruments concerned with international regulation of biomedical research the Universal Declaration on Bioethics and Human Rights (Universal Declaration) is undoubtedly the “new kid on the block.” The Universal Declaration can be looked at as a culmination of some lessons learned from the past failures of other international bioethics instruments. However, how much of an improvement it makes over other instruments remains to be seen. In June 2003, the International Bioethics Committee (IBC) of the United Nations Educational, Scientific, and Cultural Organization (UNESCO) submitted their *Report of the IBC on the Possibility of*

147. *Id.* art. 17(2).

148. PLOMER, *supra* note 56, at 18.

149. CHRБ, *supra* note 128, art. 29.

150. *Id.* art. 23.

151. *See* PLOMER, *supra* note 56, at 18.

152. Explanatory Report #2, *supra* note 142, para. 165 (“[F]acts which are an infringement of the rights contained in this Convention may be considered in proceedings under the European Convention on Human Rights, if they also constitute a violation of one of the rights contained in the latter Convention.”).

*Elaborating a Universal Instrument on Bioethics.*¹⁵³ With the blessing of the Director-General of UNESCO and its General Conference, the IBC then undertook a series of consultations with member states, drafts, and intergovernmental meetings to discuss the form and content of what would become the Universal Declaration.¹⁵⁴ Two years later, on October 19, 2005, the 33rd session of the UNESCO General Conference adopted the Universal Declaration.¹⁵⁵

As to the content of the Universal Declaration, one of the most striking differences between it and other bioethics instruments is that the Universal Declaration is “addressed to States.”¹⁵⁶ In contrast with the Nuremberg Code or the Declaration of Helsinki, which are aimed at researchers or research institutions, the Universal Declaration aims to push change on a governmental level.¹⁵⁷ The provisions for informed consent are similar to those found in the documents discussed above, including a requirement for “prior, free, express, and informed consent of the person concerned” for research-oriented treatments.¹⁵⁸ For therapeutic, preventative, or diagnostic treatments, express consent is only recommended “where appropriate.”¹⁵⁹ This kind of looser consent requirement could be exploited as research and therapeutic interventions converge. In language similar to that of the CHRB, Article 7 provides “special protection” for persons who lack capacity to consent.¹⁶⁰ Further, recognizing the special problems of vulnerable groups, perhaps especially the populations of developing countries, the Universal Declaration refuses to allow the consent of a community leader or authority or community consent to supplant the necessity for individual informed consent.¹⁶¹

153. UNESCO, *Universal Declaration on Bioethics and Human Rights*, http://portal.unesco.org/shs/en/ev.php-URL_ID=1883&URL_DO=DO_TOPIC&URL_SECTION=201.html (last visited Jan. 19, 2007).

154. *Id.*

155. *Id.*

156. U.N. Educ. Sci. & Cultural Org. [UNESCO] General Conference, Oct. 19, 2005, *Universal Declaration on Bioethics and Human Rights*, art. 1(2), UNESCO SHS/EST/BIO/06/1 [hereinafter *Universal Declaration*].

157. *See id.* art. 2(b) (stating that the instrument’s aim is “to guide the actions of individuals, groups, communities, institutions and corporations, public and private” whereas the CHRB was only directed to states of Europe).

158. *Id.* art. 6(2).

159. *Id.* art. 6(1).

160. *Id.* art. 7.

161. *Id.* art. 6(3). However, if researchers feel it is appropriate, they may seek the collective or community consent. *Id.*

The provision for ethics committees (Article 19) initially says that the committees “should be established, promoted and supported at the *appropriate level*.”¹⁶² Within that provision, it is not made clear what the “appropriate level” is. Rather, in Article 21 on “Transnational Practices”, the Universal Declaration provides that research being performed in a country other than the one where the funding source is located should be subject to dual ethical review.¹⁶³ Furthermore, the Universal Declaration insists that the terms of research agreements be established by negotiation characterized by “equal participation” by the parties.¹⁶⁴ Both of these sections seem to be aimed directly at two of the most serious problems with international clinical trials— the lack of ethical review in the host country and heavy-handedness and exploitation by the large pharmaceutical companies, many of which may have greater resources than the governments of the countries where their human subject research is performed.

As noted earlier, the Universal Declaration is addressed to states, and its drafters have seemingly left the enforcement and administration of its provisions to the state-parties. Article 22 says that “[s]tates should take all appropriate measures, whether of a legislative, administrative or other character, to give effect to the principles . . .” of the Universal Declaration.¹⁶⁵ There is no reference to any international judicial or regulatory body in any part of the Universal Declaration. Instead, the drafters seem hopeful that the benefits of “education, training and public information,” as well as international cooperation, will be sufficient protection against inappropriate and unethical research.¹⁶⁶

III. ETHICAL PROBLEMS SURROUNDING HUMAN RESEARCH IN FOREIGN COUNTRIES

This note now turns to specific ethical problems that characterize overseas clinical trials. As in Part II above, every ethical dilemma associated with such research cannot be fully addressed here. Instead, this Note looks at four issues that are, arguably, the most important and in most need to be addressed by regulation and policy.

162. *Id.* art. 19 (emphasis added).

163. *Id.* art. 21(2).

164. *Id.* art. 21(4).

165. *Id.* art. 22(1).

166. *See id.* arts. 22-24.

A. Distribution of the Costs and Benefits of International Clinical Research

The question of who benefits and who carries the burden of international clinical trials is crucial. Clearly, the pharmaceutical companies and CROs that carry out the research at lower cost, under less scrutiny and with a more abundant population of subjects are beneficiaries.¹⁶⁷ The populations of developed countries also benefit from new drugs that are developed primarily for their consumption without the need to subject themselves to the risks of clinical testing. The burdens of such research, however, fall disproportionately on the populations of the developing countries where more and more clinical trials are carried out.

There are concerns that pharmaceutical companies test drugs that are unresponsive to the needs of the local populations in the developing countries where the tests are conducted.¹⁶⁸ Bioethics documents have consistently recognized the need for the benefits of research to outweigh costs or burdens as to individual subjects.¹⁶⁹ A more recent concern has been whether subject *populations* are receiving adequate consideration before, during, and after the trials. The most recent revision of the Declaration of Helsinki says that research is “only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results.”¹⁷⁰ One method of providing some benefit to subject populations is through post-trial access to the tested products or other proven treatments. One of two new paragraphs in the Declaration of Helsinki concerns post-trial access to the best proven methods of treatment.¹⁷¹ Because of the burdens it allegedly places on the researchers and their sponsors, this addition has been one of the most contentious revisions of the Declaration in recent times.¹⁷²

The Universal Declaration also shows concern throughout for the needs of developing countries, stating that “[t]ransnational health

167. Carel Ijsselmuiden & Ruth Faden, *Research and Informed Consent in Africa*, in HEALTH AND HUMAN RIGHTS 363, 369 (Jonathan M. Mann et al. eds., 1999).

168. Jack Killen et al., *Ethics of Clinical Research in the Developing World*, in 2 NATURE REVS. IMMUNOLOGY 210, 214 (2002).

169. Declaration of Helsinki, *supra* note 104, paras. 5, 16-18; Universal Declaration, *supra* note 156, arts. 3(2), 4.

170. Declaration of Helsinki, *supra* note 104, para. 19.

171. *Id.* para. 30. A note of clarification was added to paragraph 30 in 2004, reaffirming the WMA's position on the necessity of post-trial access. *Id.* para. 30 n.2.

172. Carlson, *supra* note 109, at 702.

research should be responsive to the needs of host countries.”¹⁷³ Article 15 is explicit in declaring that the benefits of research “should be shared with . . . the international community, in particular with developing countries.”¹⁷⁴ Article 15 goes on to enumerate various forms that such benefits might take, such as provision of new products, “capacity-building facilities,” and increased access to health care.¹⁷⁵

Debate on these issues centers on whether the benefits of the trial alone provide sufficient benefit to the local population if no access to treatment was available to that population prior to the tests, and whether any harm is caused if, once the trial is over, the situation is returned to the *status quo ante*.¹⁷⁶ Research institutions and health care systems in developing countries can indeed receive some much-needed investment and improvements through hosting clinical trials. Those benefits can then be passed down to the local patients that they serve. Nevertheless, as it relates to post-trial access to the treatment itself, it seems cruel to introduce a higher standard of care to a sick population, which hopefully produces a higher standard of living, and to then abandon treatment once enough positive results begin to manifest themselves.

It should be emphasized that the question of post-trial access is separate from the related and equally important question of whether the distribution of costs and benefits between the developing world, serving largely as “guinea pigs,” and the developed world, which is the primary consumer of new drugs, is a just one. In the author’s opinion, there is something pernicious about this divorcing of costs and benefits. From a historical perspective, it is reminiscent of a relationship between the developed and the developing world that was characteristic of colonialism in previous years and in the current era by the problems of inferior labor and environmental standards and human exploitation. Post-trial access is an important goal that ought to be pursued, despite predictable opposition by the pharmaceutical companies. As recommended by the Declaration of Helsinki, any provision for post-trial access should be made part of the ethical review process that precedes the execution of any trial.¹⁷⁷ Nevertheless, the provision of additional benefits derived from

173. Universal Declaration, *supra* note 156, art. 21(3).

174. *Id.* art. 15.

175. *Id.*

176. Carlson, *supra* note 109, at 702.

177. Declaration of Helsinki, *supra* note 104, para. 30 n.2.

participation in clinical trials, such as investments in infrastructure and capacity-building, should continue to be mandated by international guidelines, and such requirements should be introduced into domestic law.¹⁷⁸

B. Ethical Imperialism or Cultural Relativism?

One of the most enduring and overarching debates regarding international clinical trials is the struggle between the search for universal principles and the need to respect diversity and pluralism. In this debate, it is important to remember that both sides are concerned about the exploitation of persons in developing countries.¹⁷⁹ The universalists are concerned that researchers will take advantage of lower standards in developing countries to perform studies that would be unethical and impermissible in developed nations.¹⁸⁰ The pluralists or relativists are worried that imposing the developed world's norms and practices on the developing world is similarly exploitative.¹⁸¹ There are two principal questions in this debate. The first question is whether the same definitions and values apply to concepts such as informed consent in different cultures and different populations. This area will be discussed specifically in the context of informed consent in Part III.C below.

The second question is whether the same standard of care should apply across cultures, especially in light of the different levels of prosperity and health care access enjoyed by those in the developed and developing worlds. The argument revolves around whether developing country research subjects are entitled to the “best current treatment,” the standard which emerges from the Declaration of Helsinki, even if the best current treatment would not normally be available to that population.¹⁸² This standard would, with few exceptions, effectively eliminate the use of a placebo control group

178. At least one group of authors has recognized the superiority of this broader definition of benefits as opposed to one focused solely on post-trial access to treatment. *See Conference on Ethical Aspects of Research in Developing Countries, Moral Standards for Research in Developing Countries: From “Reasonable Availability” to “Fair Benefits,”* 34 HASTINGS CTR. REP., 17, 22-24 (2004).

179. Christakis & Levine, *supra* note 89, at 1781-82.

180. *Id.*

181. *Id.* at 1782.

182. *See* Declaration of Helsinki, *supra* note 104, para. 29. A version of this standard was added in the 1996 revision, but the outrage surrounding it emerged after the 2000 revision. Carlson, *supra* note 109, at 700.

where an existing treatment already exists.¹⁸³ The question then essentially becomes whether the prescribed minimum is the best current treatment available anywhere, or the best current treatment available in the area where the research is taking place.¹⁸⁴

Both viewpoints in this debate have their costs and benefits. If one insists that a universal standard of care should be imposed, this substantially raises the cost of the research and eliminates the cost-saving incentive to perform research abroad. If that position is combined with a commitment to post-trial access to treatment, the cost may become prohibitive. We should not forget that the benefits of clinical trials to developing countries, such as those enumerated in Part III.A, would be withdrawn if such research became impossible. Using a current treatment, rather than a placebo, in a control group also makes discerning the scientific results more difficult; this explains one of the exceptions in the Declaration of Helsinki.¹⁸⁵

Observing a universal standard of care would certainly contribute to equality and nondiscrimination, two laudable ethical goals. However, it may not be best for the long-term health of developing countries. A contextualized standard of care, probably lower in developing countries, makes it more likely that research will be carried out in developing countries, with its attendant benefits in training and investment. These material and educational benefits could be a more efficient contribution to future health outcomes than a universal standard of care during research, especially if post-trial access is not a viable option.

While the Universal Declaration does not directly address the placebo-“best current treatment” debate, philosophically it is unabashed in its commitment to the search for “universal principles.”¹⁸⁶ Article 12 of the Universal Declaration makes clear that “cultural diversity and pluralism” should not be used to “infringe upon human dignity, human rights and fundamental freedoms, nor

183. Carlson, *supra* note 109, at 700. A “note of clarification” added to the Declaration in 2002 regarding the placebo standard added two circumstances in which placebos could be used even if a proven treatment exists: (1) for “compelling and scientifically sound . . . reasons” and (2) where the condition is minor and the control group will not be exposed to “any additional risk of serious or irreversible harm.” Declaration of Helsinki, *supra* note 104, para. 29 n.1. The CHRB Additional Protocol contains a similar but narrower exception, permitting placebo use in some situations. Additional Protocol, *supra* note 134, art. 23(3).

184. See NUFFIELD COUNCIL ON BIOETHICS, *THE ETHICS OF RESEARCH RELATED TO HEALTHCARE IN DEVELOPING COUNTRIES* 89 (2002).

185. See Declaration of Helsinki, *supra* note 104, para. 29 n.1.

186. See Universal Declaration, *supra* note 156, pmb1, art. 2(a).

upon the principles [of] this Declaration, nor to limit their scope.”¹⁸⁷ However, there is no infringement of human rights where people continue to be provided with a standard of care no less than what they had been receiving, while working to provide greater long-term benefits in the form of improved local health care systems or development of new treatments that will be made available to subjects in the future. That being said, there is never an ethical or legal excuse to go below the local or national standard of care for treating a certain disease or condition in order to prove the effectiveness of a treatment that may not immediately be made available to the subject population.¹⁸⁸

C. Informed Consent

Informed consent has justifiably been described as the “hard inner core” of medical research ethics.¹⁸⁹ As mentioned above, in the Nuremberg Code, informed consent is the first of the essential principles of bioethics.¹⁹⁰ Among the international ethical guidelines examined here, and in other ethical guidelines, there is no dispute about the necessity of informed consent in clinical trials.¹⁹¹ These instruments are also largely in agreement about the form and requirements of informed consent, even if there are differences as to some details. For example, most recognize that additional protections are necessary for those who cannot give informed consent for themselves,¹⁹² and most recognize the right to withdraw consent at any time during the research.¹⁹³

Because of the acknowledged and agreed-upon centrality of informed consent as a protection for research subjects, it is vital that informed consent is carried into practice in an effective manner wherever research occurs. Unfortunately, some data indicates that informed consent is not fully implemented in trials in the developing world. One question is whether the consent is truly informed, or

187. *Id.* art. 12.

188. See NUFFIELD COUNCIL ON BIOETHICS, *supra* note 184, at 95.

189. See SHAH, *supra* note 67, at 147.

190. Nuremberg Code, *supra* note 91, princ. 1; see SHAH, *supra* note 67, at 147.

191. Universal Declaration, *supra* note 156, arts. 6-7; Declaration of Helsinki, *supra* note 104, paras. 20, 22; CHRB, *supra* note 128, arts. 5-6, 16-17; Nuremberg Code, *supra* note 91, princ. 1.

192. Universal Declaration, *supra* note 156, art. 7; Declaration of Helsinki, *supra* note 104, paras. 24-26; CHRB, *supra* note 132, arts. 6, 17.

193. Universal Declaration, *supra* note 156, art. 6(1); Declaration of Helsinki, *supra* note 104, para. 22; CHRB, *supra* note 128, art. 5; Nuremberg Code, *supra* note 91, princ. 9.

whether it ever can be in developing countries. In one survey, only sixteen percent of researchers claimed that they verified that a subject understood the procedure.¹⁹⁴ Some researchers have expressed concerns that informing subjects in the developing world is futile due to linguistic or cultural barriers and low levels of education.¹⁹⁵

Another question is whether consent can be free in developing countries. There is anecdotal evidence that in many instances, subjects feel coerced into participating or are not told that they may withdraw at any time.¹⁹⁶ Part of this coercion can be due to financial or other incentives to stay in the trial¹⁹⁷ or because subjects simply do not feel free to say no.¹⁹⁸ Such unwillingness to refuse can originate in notions of the authority of Western doctors, the fallacy that a treatment will improve their health, lack of education, or structural issues in the culture or society.¹⁹⁹ In fact, a survey in 2001 found that among researchers working in developing countries, “[forty-five] percent reported that their low-literacy subjects *never* refused to participate.”²⁰⁰

The necessity of individual informed consent is another locus where the debate between universalism and relativism is played out. On one side are the drafters of the numerous ethical guidance instruments, who have acknowledged the necessity of informed consent. On the other side, some researchers and CROs promote the idea that certain populations in the developing world are, because of culture, more docile and malleable than Americans and therefore better candidates for research.²⁰¹ Others, including foreign physicians, believe that informed consent is a Western principle and is “unnecessary” in the context of other cultures.²⁰² It is true that in some cultures personhood is defined differently than in Western cultures, and therefore the consent of the individual will not be as

194. SHAH, *supra* note 67, at 147. Another study found that eighty percent of Haitian participants in a trial could not explain the basics of the procedure immediately after it had been explained to them. *Id.* at 148.

195. *Id.* at 151.

196. *Id.* at 148.

197. *Id.* at 149 (giving examples of powerful incentives, such as money in poor countries or food where there is an ongoing famine).

198. *See id.* at 148-49.

199. *See* Christakis & Levine, *supra* note 89, at 1784.

200. SHAH, *supra* note 67, at 148.

201. *Id.* at 149 (noting a CRO executive’s opinion that “the Chinese are not that fully emancipated as in the U.S.” and are “more willing to be guinea pigs”).

202. *Id.* at 151.

important as that of the family or the community.²⁰³ Such dilemmas have also raised concerns that the overzealous pursuit of individual consent in a collectivist society could lead to the “weaken[ing of] the social fabric.”²⁰⁴ Nevertheless, the Universal Declaration rejected any attempt to circumvent individual consent or to use diversity as a pretext to “infringe upon . . . human rights and fundamental freedoms.”²⁰⁵ This leads to a larger discussion about the universality of “human rights” that is beyond the scope of this essay.

For those who are strongly committed to the necessity of individual informed and free consent, the most obvious course of action would be to shut down trials in the developing world where such ideals could not be put into practice. This seems too extreme a remedy, especially in light of the benefits that individuals and societies in the developing world can derive from participation in clinical trials and the practical necessity of their involvement for the development of new drugs. However, any deviation from the standard of individual informed and free consent should be closely scrutinized by ethical review committees. Those committees should be well-trained and should receive the relevant evidence from researchers, anthropologists, and others to decide whether such a departure is truly necessary.

D. Deficiencies in Ethical Review

As seen in Part II, one of the ways in which international codes of ethics and current FDA regulations differ is in the requirements for ethical review. Both the Declaration of Helsinki (which the FDA has incorporated into its regulations) and the Convention on Human Rights and Biomedicine provide for ethical review only by the country where the research takes place (the host country).²⁰⁶ The Universal Declaration, on the other hand, establishes a requirement of approval by at least two review committees,²⁰⁷ one in the host country and the other in the country where the source of research funding is located.²⁰⁸

203. Christakis & Levine, *supra* note 89, at 1783.

204. *Id.* at 1784.

205. Universal Declaration, *supra* note 156, art. 12.

206. Declaration of Helsinki, *supra* note 104, para. 13; Additional Protocol, *supra* note 134, art. 9.

207. In the context of the United States, ethical review committees go by the name of institutional review boards or IRBs. *See supra* Parts II.B.

208. Universal Declaration, *supra* note 156, art. 21(2).

The idea that host countries should be the primary locus of ethical review has much to recommend it. It is not unreasonable to assume that local IRBs will be more protective of their countrymen than will a group of foreigners. Researchers as well as IRB members are often anxious to avoid allegations of “ethical imperialism” and ethnocentricity, terms that are often tossed around in the debates surrounding overseas clinical trials.²⁰⁹ Allowing the host country IRBs to handle ethical review by setting and applying their own standards is a convenient way to avoid such charges. However, the implicit assumption of such a stance is that IRBs in host countries are as capable as those in the developed sponsor countries at protecting the interests and health of research subjects, or at least at protecting them to the degree that their culture requires. There is significant evidence to the contrary.

As mentioned above, a recent survey conducted by the National Bioethics Advisory Committee found that one-fourth of all overseas clinical trials went through no ethical review at all.²¹⁰ That same inquiry found that several nations did not have ethical review committees and had no plans to create them.²¹¹ Even in those nations with committees, the review was largely ineffective, and there are several barriers that prevent ethical review from taking place in many countries. One significant problem is a lack of capacity. For example, doctors may lack training in medical ethics and good research practices.²¹² In some countries, like India, one of the current hot spots for medical research, the domestic medical association resists the imposition of minimum standards of ethics and practices.²¹³ Another difficult issue is the possibility that foreign IRBs will be unduly influenced by the resources of the pharmaceutical companies and the financial incentives being offered to their institution for participating in the study.²¹⁴ The danger is that ethics committees will

209. See Ijsselmuiden & Faden, *supra* note 167, at 364, 369.

210. SHAH, *supra* note 67, at 136.

211. *Id.* at 135.

212. *Id.* at 117–18 (giving India as an example, where one of its foremost ethical experts pointed out that “[t]here is no ethics culture in the profession” and “nobody is trained in ethics”).

213. *Id.* at 114.

214. See GRAHAM DUKES, *THE LAW AND ETHICS OF THE PHARMACEUTICAL INDUSTRY* 77–78 (2006); see generally Robert Gatter, *Conflicts of Interest in International Human Drug Research and the Insufficiency of International Protections*, 32 AM. J. L. & MED. 351, 353 (2006) (discussing generally the conflicts of interest due to the financial incentives offered to host country governments, researchers and institutions by biomedical firms).

“rubber stamp” unethical protocols, simply because they want the financial rewards of hosting clinical trials.²¹⁵

How could ethical review be carried out more effectively? One proposal would be to follow the principles set out in the Universal Declaration. This would require that the sponsoring country (most likely an industrialized Western nation with greater review capacity, resources, and higher standards) carry out its own ethical review and protect foreign patients to the same degree that they would protect domestic patients. While this would aid in harmonizing and, in general, raising standards across countries, forcing equivalent ethical review by the sponsoring country would eliminate some of the advantages that have created so much interest and activity in the area of foreign clinical trials. An alternative or additional proposal would be to have those governments, institutions, and businesses that carry out or sponsor foreign trials contribute to the development and capacity-building for ethical review in the countries where such studies are carried out. Their assistance should be both financial and technical. The objective would be to create IRBs where none currently exist and to train and monitor the committees where IRBs are already in place but are ineffective in screening out unethical and exploitative research protocols.

CONCLUSION

This note has focused on how the standards and principles set forth in international bioethics documents can be applied to the particular problems affecting international pharmaceutical clinical trials. The recommendations above are primarily ways in which governmental bodies, such as the FDA, international groups, such as the WMA and UNESCO, and private researchers can work towards the protection of human research subjects. These measures should not be employed alone, ignoring a wide range of private responses that could be employed to encourage compliance and higher standards by violating companies.²¹⁶ It is not a realistic solution to absolutely prohibit by law all overseas clinical trials, nor is that necessarily the most desirable outcome for the populations who will be the patients in the trial. However, much can be done to offer

215. See SHAH, *supra* note 67, at 135-36.

216. See generally Finnuala Kelleher, *The Pharmaceutical Industry's Responsibility for Protecting Human Subjects of Clinical Trials in Developing Nations*, 38 COLUM. J.L. & SOC. PROBS. 67 (2004) (examining private solutions such as private litigation, market pressure, “shaming”, industry codes of conduct, and accreditation).

greater protection to international human research subjects and to make the distribution of benefits from global pharmaceutical research more equitable.