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The Use of Placebos in Clinical Trials: Responsible Research or Unethical Practice?

SHARONA HOFFMAN*

I. INTRODUCTION

Developments in medical research have been occurring at a rapidly increasing rate during the past two decades.¹ Expanding budgets,² augmented computer capabilities, and new research tools have all dramatically enhanced research technology.³ Consequently, a demand exists for ever-increasing numbers of participants in clinical studies and for relaxation of the stringent requirements applicable to the recruitment and enrollment of human subjects.⁴

Accompanying the proliferation of medical research are increasing concerns about research risks. While many would like to believe that the lessons taught by the notorious Tuskegee syphilis studies⁵ and the horrify-

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1. Beverly Woodward, *Challenges to Human Subject Protections in US Medical Research*, 282 JAMA 1947, 1948 (1999).

2. See Harold Y. Vanderpool, *Introduction and Overview: Ethics, Historical Case Studies, and the Research Enterprise*, in *THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS: FACING THE 21ST CENTURY* 13 (Harold Y. Vanderpool ed., 1996) ("[F]unding for biomedical research from federal, state, local, philanthropic, and industry sources had reached the amazing sum of \$22.5 billion by 1990.").

3. Woodward, *supra* note 1, at 1948.

4. *Id.*; see also Kurt Eichenwald & Gina Kolata, *Drug Trials Hide Conflicts for Doctors*, N.Y. TIMES, May 16, 1999, at 1 (attributing the proliferation of drug trials in the 1990s to managed care and the restrictions it placed on drug prices). Since drug companies were limited in the prices they could charge for each drug, they opted to increase the number of drugs they sold in order to maintain profitability. Thus began the industry's "rush to drug development." *Id.*

5. Researchers in the United States studied the long-term effects of syphilis infection in African American males by withholding treatment from the subjects even after it was well known that penicillin could cure the disease. WILLIAM J. CURRAN ET AL., *HEALTH CARE LAW AND ETHICS* 99 (5th ed. 1998).

ing Nazi death camp experiments⁶ have been fully learned, it is clear that biomedical research in the United States is not free of abuse. In recent years, the United States Office for Protection from Research Risks (OPRR)⁷ restricted or suspended research activities at numerous institutions because of inappropriate practices.⁸ Clinical studies in which some participants receive placebos rather than active therapy are often of particular concern because of the possible adverse consequences for individuals who are deprived of treatment. It is these studies that constitute the focus of this Article.

The Latin word *placebo* means "I shall please,"⁹ though placebos are far from universally pleasing in the medical research context.¹⁰ The inclusion of placebos in trials focusing on previously untreatable conditions, that is, ailments for which there is no standard therapy, is often not controversial and is accepted as ethical in this Article.¹¹ However, the use of placebos in other circumstances has encountered increasing opposition in recent years. Critics of randomized placebo-controlled clinical trials that test medication for conditions for which there is known treatment contend that it is always unethical to deprive patients of available therapy.¹² By contrast, proponents of placebos argue that placebo-controlled studies are

6. See discussion *infra* Part IV.A.

7. In June of 2000 this office became the Office for Human Research Protections ("OHRP"), a part of the Department of Health and Human Services. See 65 Fed. Reg. 37,136-37 (June 13, 2000).

8. Woodward, *supra* note 1, at 1949 (reporting violations at eight institutions); see also Marlene Cimonis, *FDA Cites Violations, Halts Human Gene Therapy Work at Penn*, THE PLAIN DEALER, Jan. 22, 2000, at 12-A, available at LEXIS, News Library, Clevpd File; Jay Reeves, *Order Suspends University's Medical Research*, THE PLAIN DEALER, Jan. 22, 2000, at 12-A, available at LEXIS, News Library, Clevpd File (reporting that the government order could temporarily affect up to 25% of research studies conducted at the University of Alabama at Birmingham).

9. 4 WARREN THOMAS REICH, *ENCYCLOPEDIA OF BIOETHICS* 1951 (rev. ed. 1995).

10. Placebos are used in some research studies as a mechanism of comparison for the experimental treatment. While some patients are given the experimental treatment, others are given a placebo to determine whether the therapy being tested provides patients with an actual medical benefit. These studies are called "placebo-controlled" studies. 21 C.F.R. § 314.126(b)(2)(i) (1999). In other clinical trials, the experimental treatment is compared to standard therapy, that is, treatment that already exists for the condition in question. These are called "active controlled" studies. 21 C.F.R. § 314.126(b)(2)(iv) (1999).

11. See Benjamin Freedman et al., *Placebo Orthodoxy in Clinical Research I: Empirical and Methodological Myths*, 24 J. L. MED. & ETHICS 243, 243 (1996) (stating that the authors "believe that first-generation treatments, designed for previously untreatable conditions, should be tested against placebo before receiving regulatory approval"). Some may argue that all participants in a clinical trial should receive the experimental therapy if it has any hope of helping them. This argument was made with respect to medications for AIDS when they were initially tested. See Martin Delaney, *The Case for Patient Access to Experimental Therapy*, 159 J. INFECTIOUS DISEASES 416, 416 (1989). However, since study results are often difficult to interpret without a placebo comparison, failing to use placebo controls is likely to hinder the development of effective therapy. Also, since the efficacy and side effects of the experimental intervention are unknown, giving it to all participants in the trial may endanger more people than necessary.

12. See, e.g., Freedman et al., *supra* note 11, at 244 (stating that "[s]econd-generation treatments . . . should be tested against accepted therapy, rather than, at present, against placebo").

cheaper, easier to interpret, and provide more definitive results than active-controlled trials.¹³

The use of placebo controls in studies involving treatable conditions raises questions relating to the ethical principles of beneficence and human autonomy.¹⁴ Beneficence dictates that physicians must avoid harming human subjects and must maximize potential benefits while minimizing risks to study participants.¹⁵ It is arguable that the doctrine of beneficence militates against the inclusion of placebos in clinical trials under most if not all circumstances. Since patients assigned to a placebo control arm receive no treatment for their symptoms and underlying disease, it is, according to some, unethical to construct placebo-controlled studies.¹⁶ By contrast, the doctrine of human autonomy might support unrestricted use of placebo controls even when effective therapy is available for the condition in question.¹⁷ Arguably, patients, as autonomous, self-determining agents, should be free to choose to participate in studies in which they might forgo treatment even at the risk of sacrificing their own health and welfare.

This Article supports a compromise position. It suggests that the use of placebo controls is ethical and appropriate in limited circumstances so long as adequate safeguards are implemented to protect human subjects. If the experimental drug constitutes a first-line treatment for a previously untreatable disease or patient population, the new medication could, without objection, be compared to a placebo since no standard therapy is available.¹⁸ On the other hand, placebos should not be utilized in studies relating to serious, irreversible, or life-threatening conditions for which effective therapy exists.¹⁹ However, where the subject would not be exposed to the threat of death, disability, severe pain, or long-term harm by assignment to the placebo arm of a clinical trial, the use of placebos should be permitted if the following conditions are met: (1) each patient is carefully and frequently monitored; (2) early escape mechanisms exist for patients who suffer adverse consequences related to the lack of active therapy; (3) the clinical trial's duration is as short as possible; and (4) each participant

13. See U.S. FDA, FOOD AND DRUG ADMINISTRATION INFORMATION SHEETS: GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS AND CLINICAL INVESTIGATORS 7 (1998), available at <http://www.fda.gov/oc/oha/IRB/toc7.html> [hereinafter FDA INFORMATION SHEET]; see also Stuart L. Nightingale, *Challenges in Human Subject Protection*, 50 FOOD & DRUG L.J. 493, 498 (1995). See *supra* note 10 and *infra* Part II.B for an explanation of the terms "placebo-controlled" and "active-controlled."

14. Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 44 Fed. Reg. 23,192 23,192 23,194 (Dep't of Health, Educ. & Welfare Apr. 18, 1979) [hereinafter Belmont Report].

15. *Id.* at 23,194.

16. See discussion *infra* Parts II.C & V.A.

17. See discussion *infra* Part V.B.

18. Freedman et al., *supra* note 11, at 250.

19. Nightingale, *supra* note 13, at 498.

is clearly informed of and consents to the possibility that he or she will receive a placebo rather than standard or experimental treatment.

These safeguards should be incorporated into the federal regulations promulgated by the Food and Drug Administration ("FDA") and the Department of Health and Human Services ("DHHS"). With these protections in place, individuals could make autonomous decisions, while at the same time investigators could fulfill their duties to promulgate beneficence in medical research.

The Article will begin in Part II with a description of placebos and a discussion of their benefits and risks. Part III will review federal regulations regarding clinical trials and placebo use. Part IV will focus upon general ethical guidelines delineated in the Nuremberg Code,²⁰ the Declaration of Helsinki,²¹ and the Belmont Report.²² Part V will analyze the challenges of formulating guidelines specifically relating to the use of placebos. Discussion will focus on the concepts of beneficence and autonomy, on the role of the physician, and on institutional oversight. Finally, Part VI will provide specific recommendations regarding proper usage of placebo controls and the relevant regulations that should be developed by the FDA and DHHS.

II. PLACEBO CONTROLS

A. *What Are Placebo Controls?*

Clinical trials for new drugs often include placebo controls.²³ A control in a biomedical research study provides a mechanism by which to compare results from subjects taking an experimental intervention to results from a group that is not receiving the treatment being studied.²⁴

Researchers utilize a variety of different controls in their studies. When a placebo control is utilized, the experimental drug is compared with an inactive substance that is designed to look like the test drug.²⁵ A second design, a dose-comparison control trial, involves at least two different doses of the same drug so that the safest and most effective dosage can be determined.²⁶ A no-treatment control allows investigators to measure the

20. TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10, 181-82 (photo. reprint 1977) (1949) [hereinafter NUREMBERG CODE].

21. WORLD MED. ASS'N, DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (amended 2000), available at http://www.wma.net/e/policy/17-c_e.html [hereinafter DECLARATION OF HELSINKI].

22. Belmont Report, *supra* note 14 at 23, 192.

23. See Kenneth J. Rothman & Karin B. Michels, *The Continuing Unethical Use of Placebo Controls*, 331 NEW ENG. J. MED. 394, 395 (1994).

24. Nancy K. Plant, *Adequate Well-Controlled Clinical Trials: Reopening the Black Box*, WIDENER L. SYMP. J. 267, 270 (1996).

25. 21 C.F.R. § 314.126(b)(2)(i) (1999).

26. 21 C.F.R. § 314.126(b)(2)(ii) (1999).

effectiveness of the experimental drug by comparing the medical progress of patients receiving the new medication to the condition of those receiving no active treatment and no placebo.²⁷ By contrast, in clinical trials in which an active control²⁸ is used, patients who do not receive the experimental treatment are given standard therapy consisting of an active agent.²⁹ Finally, investigators may also use historical controls, assessing the results of the experimental treatment in light of previously gathered data regarding the natural progression of the disease or the outcome of active treatment.³⁰

Recently, placebo controls have been utilized not only in drug studies but also in studies involving surgical procedures.³¹ In these trials the placebo control takes the form of a sham surgery.³² Physicians anesthetize patients in the control group and make an incision that will leave scarring but do not perform the actual surgical procedure being tested in the study.³³ This form of "placebo," therefore, not only deprives the subject of active treatment, but also exposes the patient to risks associated with anesthesia and a deep incision.

In a randomized placebo-controlled clinical trial, each participant is told that there is a certain chance, for example, fifty percent or thirty-three percent, that he or she will receive an inert substance or a sham surgery.³⁴

27. 21 C.F.R. § 314.126(b)(2)(iii) (1999). Protocols that compare no treatment to active treatment raise some of the same questions as those that compare a placebo to a new therapy. There is one very significant difference, however. A study designed with an arm that provides no treatment to patients does not attempt to deceive participants or disguise the nature of the therapy they are receiving. Patients randomly assigned to the no-treatment control arm are fully aware that the study is of no direct medical benefit to them. The patients can request to withdraw from the trial as soon as they decide they wish to receive treatment. In contrast, patients in a placebo-controlled trial are not told whether they are receiving a placebo or an active therapy, and investigators make deliberate efforts to conceal from participants in the placebo arm the fact that they are receiving an inactive agent or a sham surgery. Subjects thus have far less information to assist them in deciding whether or when to discontinue enrollment in the clinical study.

Since investigators often wish to test whether a placebo effect is associated with the experimental therapy, however, placebo controls can provide results that are far superior to those of no-treatment controls. See discussion *infra* Part II.B. Consequently, this Article focuses on the use of placebo controls in clinical trials and does not urge that no treatment controls be used instead. Nevertheless, some of the arguments can logically be extended to trials involving no treatment.

28. Active controls can be defined as agents that are "of established efficacy at the dose used and under the conditions of the study." International Conference on Harmonisation; Choice of Control Group in Clinical Trials, 64 Fed. Reg. 51,767, 51,775 (Dep't of Health & Human Servs. Sept. 24, 1999). Active controls generally consist of agents "acceptable in the region to which the studies will be submitted for the same indication at the dose being studied." *Id.* However, in some cases, active controls themselves are of uncertain benefit. See *id.*

29. 21 C.F.R. § 314.126(b)(2)(iv) (1999).

30. 21 C.F.R. § 314.126(b)(2)(v) (1999).

31. See Margaret Talbot, *The Placebo Prescription*, N.Y. TIMES MAG., Jan. 9, 2000, at 34; Thomas B. Freeman et al., *Use of Placebo Surgery in Controlled Trials of a Cellular-Based Therapy for Parkinson's Disease*, 341 NEW ENG. J. MED. 988, 988 (1999).

32. See Talbot, *supra* note 31, at 34; Freeman et al., *supra* note 31.

33. Freeman et al., *supra* note 31, at 989-90.

34. See Robert J. Levine, *The Use of Placebos in Randomized Clinical Trials*, 7 IRB 1, 1 (1985).

Assignment to either the treatment or placebo group is not calculated based on any factor specific to the patient, but rather occurs on a random basis.³⁵ Prospective subjects are asked to agree to "blinding," and therefore they remain ignorant of whether they are receiving the experimental treatment or a placebo.³⁶ Many studies involve "double blinding," whereby neither the patient nor the patient's doctor knows which therapy the patient is receiving.³⁷ Double blinding is favored under the theory that, in order to determine the true effects of an experimental treatment, conscious and unconscious biases on the part of both patients and physicians must be minimized so that the study results are not skewed by various psychological factors.³⁸

B. *The Benefits of Placebo Controls*

Given the alternatives available to those designing clinical trials, one must ask why investigators do not always utilize active controls. Many researchers, however, believe that placebo-controlled trials are more informative than other types of studies.

FDA officials generally consider placebo controls to be the "gold standard" for clinical trials.³⁹ In its "Guidelines for the Clinical Evaluation of Anti-Inflammatory and Antirheumatic Drugs," for example, the agency requires the inclusion of a placebo arm when new drug applications are submitted for fixed-dose combinations of nonsteroidal anti-inflammatory medications with codeine.⁴⁰ Likewise, the FDA refused to approve a new beta-blocker for use in treatment of angina pectoris because the drug had not been compared with a placebo, even though effective therapy already existed for the condition.⁴¹

Like the FDA, the American Medical Association ("AMA") advocates the continued use of placebo controls.⁴² It states that "[p]lacebo controls are an important part of medicine's commitment to ensuring that the safety and efficacy of new drugs are sufficiently established."⁴³ Moreover, the AMA emphasizes that the existence of effective treatment does not rule out the use of placebos, since they can "safely provide valuable data" under

35. Plant, *supra* note 24, at 271.

36. *Id.* at 272; Levine, *supra* note 34, at 1.

37. Plant, *supra* note 24, at 272; Levine, *supra* note 34, at 1.

38. Plant, *supra* note 24, at 272.

39. Rothman & Michels, *supra* note 23, at 395.

40. *Id.*

41. *Id.*

42. AM. MED. ASS'N COUNCIL ON ETHICAL & JUDICIAL AFFAIRS, OPINION NO. E-2.075, THE USE OF PLACEBO CONTROLS IN CLINICAL TRIALS (1996), available at <http://www.ama-assn.org/ama/pub/category/2513.html> [hereinafter CEJA OPINION].

43. *Id.*

appropriate circumstances.⁴⁴

Proponents of placebo-controlled clinical trials assert that active control trials are often difficult to interpret because both the active control and the experimental treatment may have significant placebo effects.⁴⁵ Medications for pain, nausea, insomnia, depression, and many other conditions are often effective in large part because of their placebo effect rather than their active ingredients.⁴⁶ The very fact that some medication has been received may relieve the patient of symptoms, since the patient's anxiety about the condition is diminished, and the patient is convinced that he or she should experience improvement.

Recently, a promising new drug for depression, MK-869 produced by Merck, failed in efficacy tests because of "the curse of the placebo effect," which was evident when patients who received a dummy pill had unexpectedly good results.⁴⁷ Similarly, while 75% of patients improved after receiving a new allergy vaccine developed by the British company, Peptide Therapeutics, exactly the same number of subjects experienced relief after taking inert tablets.⁴⁸ Even more surprisingly, in a study regarding VEGF, a genetically engineered heart drug produced by Genentech, the placebo performed better than the active agent.⁴⁹ Some researchers assert that many antidepressant drugs are essentially sophisticated placebos.⁵⁰

The placebo effect has also been evident in clinical studies involving sham surgery. In a clinical trial of surgery to relieve arthritic knee pain, for example, all of the patients who underwent fake procedures reported significantly less pain thereafter.⁵¹ Similarly, Parkinson's disease patients who underwent a simulated procedure of fetal tissue transplantation into the brain experienced significant improvement, though patients who actually received the fetal tissue implants showed even greater progress.⁵²

Experts emphasize the importance of the placebo effect. According to

44. *Id.* The AMA cautions that investigators conducting placebo-controlled studies must be extremely thorough in obtaining informed consent from patients, must carefully evaluate the need to use a placebo control, and should minimize the amount of time during which placebos are given to the patients. *Id.*

45. Nightingale, *supra* note 13, at 498.

46. Placebo effect is the improvement in the patient's condition that results from the symbolic component of the healing encounter rather than the pharmacological or physiological properties of the medication used. REICH, *supra* note 9, at 1952.

47. Martin Enserink, *Can the Placebo Be the Cure?*, 284 SCIENCE 238 (1999).

48. Talbot, *supra* note 31, at 37.

49. *Id.* Patients who received low doses of VEGF could walk twenty-six seconds longer than they had before treatment two months earlier, those receiving high doses, walked thirty-two seconds longer, and those given the placebo walked forty-two seconds longer. *Id.*

50. Enserink, *supra* note 47, at 238.

51. Talbot, *supra* note 31, at 35. The trial involved only ten patients and thus did not offer definitive conclusions regarding the efficacy of the arthroscopic surgery. A larger trial involving 180 subjects was subsequently commenced. *Id.*

52. *Id.* at 36.

one source, between 35 and 75% of research subjects derive some benefit from taking inactive agents in biomedical studies.⁵³ Thus, arguably, only a clinical trial that utilizes a placebo control can determine whether the new drug has pharmacological and physiological benefits rather than solely or primarily psychological ones. If subjects that receive placebos do as well as those being given active treatment, researchers can conclude that the active ingredients in the experimental medication or the real surgical procedures are of no significant beneficial value. To the extent that patients receiving active therapy are improving, they are doing so as a result of the intervention's placebo effect.

In placebo-controlled studies investigators attempt to show that there is a difference between the new therapy and the placebo.⁵⁴ Researchers hope to prove that those receiving the investigational treatment enjoy a medical benefit and that patients in the control arm of the study are not experiencing similar improvement.⁵⁵ By contrast, in clinical trials with an active control, a finding of no difference between the new treatment being tested and the traditional therapy given in the control arm is considered evidence that the new intervention is effective.⁵⁶ Presumably, if patients do as well with the investigational treatment as they do with standard therapy, the new medication or procedure must be beneficial in treating the condition in question.

Consequently, the two types of study designs provide opposite incentives for researchers. A clinical trial utilizing a placebo control, which seeks to show a difference between the results in the two arms of the study, creates powerful incentives for researchers to avoid any carelessness and achieve a high level of accuracy.⁵⁷ Researchers hope to prove that patients receiving the experimental medication consistently do better than those in the placebo group.⁵⁸ Even small differences in results may justify approval of the drug by the FDA and subsequent marketing of the medication. By contrast, active control studies that are intended to show no difference between the two treatments do not generate similar incentives to avoid sloppiness.⁵⁹ Researchers do not seek to show the same consistency of results for patients in one arm of the study or the other or to track minute differences in the consequences of treatment.

The FDA explains that "there are numerous ways of conducting a study that can obscure differences between treatments, such as poor diag-

53. *Id.*

54. See FDA INFORMATION SHEET, *supra* note 13, at 7.

55. See *id.*

56. See *id.*

57. *Id.*; BARUCH A. BRODY, ETHICAL ISSUES IN DRUG TESTING, APPROVAL, AND PRICING 114 (1995).

58. See FDA INFORMATION SHEET, *supra* note 13, at 7; BRODY, *supra* note 57, at 114.

59. BRODY, *supra* note 57, at 114.

nostic criteria, poor methods of measurement, poor compliance, medication errors, or poor training of observers.”⁶⁰ Consequently, an absence of therapeutic difference between the experimental treatment and standard therapy in an active-controlled trial may be attributable to failure on the part of participants to take prescribed doses of a drug, failure on the part of physicians to recommend appropriate dosages, or a variety of other errors.⁶¹

In addition, a finding of no difference in an active control study may mean that both substances are effective for a particular patient population, that neither medication was effective, or that the study for some reason was unable to distinguish between effective and ineffective agents.⁶² According to the FDA, researchers cannot determine the value of a test drug in an active control trial without ascertaining that the active control itself would have been superior to a placebo for the individuals participating in the trial.⁶³

It is possible that unexpected results of particular studies are related to the peculiarities of the subject population rather than the efficacy of the experimental intervention itself. For some patients, conventional therapy produces no positive results or perhaps even an aggravation of symptoms. In such circumstances, the use of standard therapy in the control arm would obfuscate the results of the research. While patients in the active control arm would be expected to show improvement, in reality, their condition would remain static or even deteriorate because they do not have the anticipated, positive reaction to conventional treatment. Consequently, it would be necessary to compare the experimental medication to a placebo or a no-treatment control for these patients.

In fact, not every study is designed to determine whether a particular treatment is as potent as existing therapy. Some studies attempt to identify alternatives to drugs with harsh side effects that cannot be tolerated by many patients.⁶⁴ Although the test drug is known to be somewhat less potent than already available medication, such studies attempt to show that it is better than no intervention and can be taken by those who have severe adverse reactions to existing treatment.⁶⁵ In these clinical trials it would be unethical to require subjects in a control group to take a treatment that they cannot tolerate simply in order to compare its effects to those of the experimental drug. If an active control were to be used with patients known to have an adverse reaction to existing therapy, the control group patients could suffer extremely uncomfortable or even life-threatening consequences.

60. FDA INFORMATION SHEET, *supra* note 13, at 7.

61. *Id.*

62. *Id.*; BRODY, *supra* note 57, at 115.

63. FDA INFORMATION SHEET, *supra* note 13, at 7.

64. See generally Freedman et al., *supra* note 11, at 247-48.

65. See *id.*

Similarly, some trials may be specifically designed to find an alternative for patients who have no response to conventional therapy, and thus, for subjects in these trials, existing treatments are equivalent to placebos, since they have no beneficial biological effect.⁶⁶ In such cases too it would be appropriate to utilize a placebo in order to determine whether the new therapy is superior to no medical intervention whatsoever.

Like active controls, historical controls are often difficult to interpret. It is at times impossible to verify that historical control groups are comparable to the subjects in the clinical trial with respect to variables that could affect outcomes.⁶⁷ Those treated for the disease in the past, for example, may have had other medical conditions or different degrees of illness severity, and all of their relevant medical data may not be available to investigators. Consequently, historical control designs are used in clinical trials only in limited circumstances, most notably where the disease in question has a high and predictable mortality rate or where the effect of the treatment is self evident, as in the case of general anesthesia.⁶⁸

Placebo controls are often preferred over active or historical controls not only for their scientific advantages, but also for economic reasons. Because active therapy can be very costly, active control trials are at times small and thus do not yield statistically significant and clinically meaningful results.⁶⁹ Historical control studies, in which each subject receives the experimental therapy, can also be very costly. Employing a placebo control is generally far less expensive since the placebo contains no active substance. This allows researchers to utilize large groups and to obtain statistically significant results quickly.⁷⁰

Despite the considerable benefits offered by placebo controls, placebos remain controversial, and their use is often debated by scientists and ethicists. As discussed below, some commentators assert that the use of placebo controls is harmful to subjects and scientifically unsound.

C. *Concerns About Placebo Utilization*

The most obvious disadvantage of placebo controls is that they deprive human subjects of potentially beneficial treatment.⁷¹ If the clinical trial involves a condition that is treatable, patients assigned to the placebo control arm forgo treatment that they could otherwise receive. Those who obtain neither the experimental intervention nor conventional treatment

66. *See id.*

67. 21 C.F.R. § 312.126(b)(2)(v) (2000); FDA INFORMATION SHEET, *supra* note 13, at 7.

68. *See* 21 C.F.R. § 312.126(b)(2)(v) (2000); FDA INFORMATION SHEET, *supra* note 13, at 7.

69. *See* FDA INFORMATION SHEET, *supra* note 13, at 7; BRODY, *supra* note 57, at 114.

70. *See* Jill Wechsler, *Placebos and Subject Protection*, APPLIED CLINICAL TRIALS, June 1998, at 28, 29.

71. Benjamin Freedman et al., *Placebo Orthodoxy in Clinical Research II: Ethical, Legal, and Regulatory Myths*, 24 J. L. MED. & ETHICS 252, 253 (1996).

because they are members of the placebo control group may fare more poorly than those in the active therapy arm or arms of the clinical trial. For example, in one nine month trial involving patients with chronic schizophrenia, 66% of the placebo group relapsed, while only 8% of the patients receiving fluphenazine decanoate suffered relapses.⁷² It is arguable that even placebo-controlled clinical trials relating to benign conditions, such as allergies, inflict harm on participants receiving inert substances, since from the patients' own perspectives, their symptoms are troubling and should be relieved.⁷³

Some commentators note that the placebo effect itself can be variable.⁷⁴ The effectiveness of placebos has been shown to depend at times upon the color and form of the substance.⁷⁵ Different colors and forms of placebos have generated different placebo effects for various conditions.⁷⁶ Subjects taking red capsules, for example, might not react the same as those receiving blue tablets. The results of placebo-controlled clinical trials, therefore, may vary depending on the color, type, and dose of the placebo, and placebos, arguably, may not always serve as a reliable baseline against which to compare an experimental drug's biological effectiveness.⁷⁷

Finally, critics assert that placebo-controlled trials reveal information that is far less valuable than that learned from active-control studies. The following is a lucid explanation of this argument: "Placebo-controlled trials ask, 'Is the new treatment better than nothing?'; active-control trials ask, 'Is the new treatment (at least) as good as what is currently being used?' Only the latter question is truly responsive to the needs of clinicians and their patients."⁷⁸

According to some, placebo-controlled trials could lead to the approval of treatments that are far inferior to already existing therapy because the experimental medication is not compared to standard treatment.⁷⁹ One article has gone as far as to compare placebo-controlled clinical trials to "flinging a glass of water at a burning building."⁸⁰ Just as a glass of water

72. *Id.*

73. *Id.* at 254.

74. See Freedman et al., *supra* note 11, at 244.

75. *Id.*

76. *Id.* The authors use the example of an investigator who tests a drug, a blue tablet, taken three times daily, against an identical placebo and finds that the drug is effective when compared to the placebo. *Id.* They argue that it is possible that a drug with a different presentation, for example, a red capsule, "would not prove superior to other matched placebos." *Id.* Therefore, the investigator's clinical trial, arguably, did not prove that the experimental drug generally had a biological effect that was superior to that of a placebo, only that it was superior to a placebo in the particular form of a blue tablet. *Id.*

77. See *id.*

78. *Id.* at 250.

79. *Id.*

80. Freedman et al., *supra* note 71, at 258.

will not extinguish a large fire, a placebo-controlled trial will not lead to the development of effective new therapy, according to opponents.

These criticisms, however, ignore many of the difficulties of utilizing active controls, which were discussed above.⁸¹ To summarize, first, many clinical trials are designed to produce alternatives for patients who cannot tolerate existing therapy or who are resistant to it, even if the new treatment will not necessarily be better for all patients. Providing control group subjects in such trials with the traditional therapy that causes them to suffer harsh side effects or that is of no benefit to them would be inappropriate. In addition, active controls are themselves often misleading since active treatments are ineffective for at least some patients, interact with other drugs, or provide relief of symptoms only because of their own placebo effect. Placebo controls, which have no side effects and do not interact with other medications, can provide clearer results than other mechanisms of comparison and may allow researchers to use larger sample groups because of their low cost.⁸² Consequently, placebo controls cannot lightly be dismissed as generating inferior scientific results in all circumstances.

D. *Specific Examples of Clinical Trials Utilizing Placebo Controls in Controversial Circumstances*

Experts cite numerous examples of cases in which placebos were used in clinical trials relating to various medical conditions despite the existence of proven standard therapy for the ailments at issue. All of the studies described below have generated criticism and controversy.

1. *Studies Conducted in the United States*

One trial, reported in 1985, was designed to study the efficacy of ivermectin to treat onchocerciasis, or river blindness.⁸³ The subjects were illiterate Liberian seamen, some of whom indicated their informed consent by thumbprints.⁸⁴ The clinical trial utilized a placebo even though diethylcarbamazine had been the standard therapy for the condition for over thirty years.⁸⁵

Numerous placebo-controlled trials have been conducted to study secondary treatments for rheumatoid arthritis.⁸⁶ While all participants re-

81. See *supra* Part II.B.

82. See *supra* Part II.B.

83. See Bruce M. Greene et al., *Comparison of Ivermectin and Diethylcarbamazine in the Treatment of Onchocerciasis*, 313 NEW ENG. J. MED. 133, 133 (1985).

84. *Id.* at 133-34.

85. Rothman & Michels, *supra* note 23, at 395.

86. *Id.* (citing P. Tugwell et al., *Low-dose Cyclosporin Versus Placebo in Patients with Rheumatoid Arthritis*, 335 LANCET 1051-55 (1990); V. Johnsen et al., *Auranofin (SK&F) in Early Rheumatoid Arthritis: Results from a 24-month Double-blind, Placebo-controlled Study: Effect on Clinical and Biochemical Assessments*, 18 SCANDINAVIAN J. RHEUMATOLOGY 251-60 (1989); H.J. Williams et al., *A Controlled Trial Comparing Sulfasalazine, Gold Sodium Thiomalate, and Placebo in Rheumatoid*

ceived a primary therapy, such as nonsteroidal anti-inflammatory drugs, they were randomized to receive either a new secondary treatment or a placebo supplement.⁸⁷ These trials continued even though some secondary treatments had already been proven more effective than placebos, and the placebo group was known to be at risk for serious and irreversible degenerative changes that could, to some extent, be prevented with potent secondary therapies.⁸⁸

Placebo controls are often employed in clinical trials of antidepressant drugs for major depression, despite the acknowledged existence of effective therapy.⁸⁹ A 1992 study, for example, assigned half of the seriously depressed participants to receive paroxetine and the other half to take a placebo.⁹⁰

In several studies of a new treatment for chemotherapy-induced vomiting, the experimental drug, ondansetron, was compared with a placebo.⁹¹ The placebo was utilized even though several agents including metoclopramide, phenothiazines, substituted bensamides, corticosteroids, and benzodiazepines are available to treat the condition.⁹²

New drugs for congestive heart failure are often evaluated against placebos in clinical trials even though angiotensin-converting-enzyme inhibitors are accepted as standard therapy for this serious disease.⁹³ Similarly, clinical trials of new drugs for mild to moderate hypertension commonly use placebo controls despite the proven effectiveness of many agents for

Arthritis, 31 ARTHRITIS & RHEUMATISM 702-13 (1988); D.E. Trentham et al., *Effects of Oral Administration of Type II Collagen on Rheumatoid Arthritis*, 261 SCIENCE 1727-30 (1993)).

87. *Id.*

88. *Id.*

89. *Id.*

90. K. Rickels, et al., *The Efficacy and Safety of Paroxetine Compared with Placebo in Outpatients with Major Depression*, 53 J. CLINICAL PSYCHIATRY 30, 30-32 (Supp. 1992). Some patients may have found an active control using standard therapy to be objectionable. Many drugs for depression have severe side effects that are not well tolerated by patients. Thus, some patients may be willing to try an experimental drug or to take a placebo but would be unwilling to accept standard treatment. See discussion *supra* Part II.B.

91. Rothman & Michels, *supra* note 23, at 395 (citing T. M. Beck et al., *Efficacy of Oral Ondansetron in the Prevention of Emesis in Outpatients Receiving Cyclophosphamide-Based Chemotherapy*, 118 ANN. INTERN. MED. 407, 407-13 (1993); David R. Gandara et al., *The Delayed-Emesis Syndrome from Cisplatin: Phase III Evaluation of Ondansetron Versus Placebo*, 19 SEMINARS IN ONCOLOGY 67, 67-71 (Supp. 1992); Luigi. X. Cubeddu et al., *Efficacy of Ondansetron (GR 38032F) and the Role of Serotonin in Cisplatin-Induced Nausea and Vomiting*, 322 NEW ENG. J. MED. 810, 810-16 (1990)).

92. Rothman & Michels, *supra* note 23, at 395.

93. *Id.* (citing Alan J. Cowley & Damian J. McEntegart, *Placebo-Controlled Trial of Flosequinan in Moderate Heart Failure: The Possible Importance of Aetiology and Method of Analysis in the Interpretation of the Results of Heart Failure Trials*, 38 INT'L J. CARDIOLOGY 167, 167-75 (1993); H. Kelbaek et al., *Angiotensin Converting Enzyme Inhibition at Rest and During Exercise in Congestive Heart Failure*, 14 EUR. HEART J. 692, 692-95 (1993); Milton Packer et al., *Double-Blind, Placebo-Controlled Study of the Efficacy of Flosequinan in Patients with Chronic Heart Failure*, 22 J. AM. C. CARDIOLOGY 65, 65-72 (1993)).

high blood pressure.⁹⁴

Placebos are also often utilized in research relating to drug treatment programs even though methadone is known to be effective in treating opiate addiction.⁹⁵ In two studies patients were randomized to receive either a placebo or buprenorphine, the experimental drug.⁹⁶ One study was terminated prematurely because buprenorphine proved substantially superior to placebo, and the patients receiving the placebo suffered extreme discomfort as their heroin withdrawal progressed with no medication to relieve their symptoms.⁹⁷ Had buprenorphine been compared instead to the standard therapy of methadone in an active-controlled study, the patients would have been spared much suffering.

One particularly controversial study involved Parkinson's disease patients who were enrolled in a randomized, controlled trial.⁹⁸ Some patients underwent brain surgery for the purpose of fetal tissue transplantation, while others underwent a sham surgery in which general anesthesia was administered to them and a partial hole was drilled in their skulls.⁹⁹ Patients were thus subjected to an operation that would be of no therapeutic benefit despite the risks of anesthesia and invasive surgical procedures.¹⁰⁰

2. Placebo-Controlled Trials in Developing Countries

Placebo-controlled clinical trials in developing countries have generated significant debate in recent years.¹⁰¹ Particular attention has been focused on placebo-controlled studies of treatments to prevent mother-to-child (also known as "vertical") transmission of the human immunodeficiency virus ("HIV") that are conducted in Third World countries.¹⁰²

In 1994, a clinical trial in the United States, AIDS Clinical Trials

94. *Id.* (citing A.A. Carr et al., *Once-Daily Verapamil in the Treatment of Mild-to-Moderate Hypertension: A Double-Blind Placebo-Controlled Dose-Ranging Study*, 31 J. CLINICAL PHARMACOLOGY 144, 144-50 (1991); L.P. Svertkey et al., *Double-Blind Comparison of Doxazosin, Nadolol, and Placebo in Patients with Mild-to-Moderate Hypertension*, 43 CURR. THER. RES. 969, 969-78 (1988); D. Torvik & H.P. Madsbu, *Multicentre 12-Week Double-Blind Comparison of Doxazosin, Prazosin and Placebo in Patients with Mild to Moderate Essential Hypertension*, 21 BRIT. J. CLINICAL PHARMACOLOGY 69s, 69s-75s (Supp. 1986)).

95. *See Clinical Trial Subjects: Adequate FDA Protections? Hearing Before the Committee on Government Reform and Oversight, House of Representatives*, 105th Cong. 195 (1998) (statement of Peter Lurie & Sidney M. Wolfe, Public Citizen's Health Research Group, Institute for Social Research, University of Michigan) (citing Rolley E. Johnson et al., *A Placebo Controlled Clinical Trial of Buprenorphine as a Treatment for Opioid Dependence*, 40 DRUG ALCOHOL DEPENDENCE 17-25 (1995)).

96. *See id.*

97. *See id.* at 195-96.

98. *See* Freeman et al., *supra* note 31, at 988.

99. *See id.* at 989-90.

100. *See id.*; *see also* Talbot, *supra* note 31, at 34. The article discusses studies that include sham arthroscopic knee surgeries to relieve arthritis pain.

101. *See* Praphan Phanuphak, *Ethical Issues in Studies in Thailand of the Vertical Transmission of HIV*, 338 NEW ENG. J. MED. 834, 834 (1998).

102. *See id.*

Group ("ACTG") Study 076, revealed that the drug zidovudine ("AZT") reduced the vertical HIV transmission rate by two thirds, from 25.5% to 8.3%.¹⁰³ The standard of care quickly evolved into a regimen requiring prescriptions of AZT for affected pregnant women during the last two trimesters of pregnancy, administration of an intravenous bolus of AZT during delivery, and AZT for the newborn for the first six weeks of life.¹⁰⁴ Unfortunately, the cost of the treatment, \$800 per patient for the drug, was affordable only in industrialized nations.¹⁰⁵ In Uganda, which has a very high rate of mother-to-child HIV transmission, the cost of the AZT treatment represents 400 times the yearly per capita expenditure on health care.¹⁰⁶

The World Health Organization ("WHO") urged that studies begin immediately to determine whether significantly cheaper alternatives to the AZT regimen could achieve some reduction in the rate of maternal-fetal HIV transmission.¹⁰⁷ Sixteen placebo-controlled trials were commenced in developing countries, including the Ivory Coast, Uganda, Tanzania, Malawi, Ethiopia, Burkina Faso, Zimbabwe, Kenya, Thailand, Dominican Republic, and South Africa.¹⁰⁸ Nine studies were funded by the U.S. Centers for Disease Control and Prevention ("CDC") or the National Institutes of Health ("NIH"), five were financed by other governments, and one was paid for by the United Nations Program on Acquired Immune Deficiency Syndrome.¹⁰⁹

Various alternatives to the standard AZT treatment were studied in the different trials. In Thailand, for example, a short course of AZT, for a duration of two to four weeks, was compared to a placebo control.¹¹⁰ In South Africa, researchers conducting one study assessed a combination of AZT and 3TC given for a short time before, during, or after delivery.¹¹¹ A second study was designed to evaluate the effect of vitamin A supplementation.¹¹² Both trials were double-blinded, randomized control trials with placebo arms.¹¹³ In February of 1998, when the Thailand study revealed that a four week course of AZT reduced HIV transmission rates by 50%, CDC, NIH and the United Nations Program on AIDS recommended the

103. Ronald Bayer, *The Debate over Maternal-Fetal HIV Transmission Prevention Trials in Africa, Asia, and the Caribbean: Racist Exploitation or Exploitation of Racism?*, 88 AM. J. PUB. HEALTH 567, 567 (1998).

104. *Id.*

105. *Id.*

106. *Id.*

107. *Id.*

108. *Id.*

109. *Id.*

110. See Phanuphak, *supra* note 101, at 835.

111. Salim S. Abdool Karim, *Placebo Controls in HIV Perinatal Transmission Trials: A South African's Viewpoint*, 88 AM. J. PUB. HEALTH 564, 564 (1998).

112. *Id.*

113. *Id.*

discontinuation of placebo usage in all vertical transmission studies, and hundreds of women were switched from placebo arms to treatment.¹¹⁴

Proponents of the vertical transmission studies point out that the ACTG 076 AZT regimen is not affordable in developing nations.¹¹⁵ Since the ACTG 076 treatment is not the standard of care in Third World nations, women receiving the placebo control would not be deprived of any treatment otherwise available to them.¹¹⁶ Where the study was funded by local sources or the United Nations, inclusion of an active control arm was financially unrealistic.¹¹⁷ Given the high frequency of home deliveries and the failure of many women to seek prenatal care in some of the developing countries, administration of the full AZT protocol would have also been pragmatically impossible.¹¹⁸ Moreover, since the studies were designed to determine whether an alternative to the ACTG 076 regimen was better than no medical intervention at all, it was ethically appropriate, according to advocates, to utilize a placebo comparison.¹¹⁹

Nevertheless, the maternal-fetal HIV transmission trials produced significant opposition in academic circles. Several commentators issued the following warning: "Many people will hear in these experiments echoes of the notorious Tuskegee syphilis study. . . . This time, the people of color affected are babies from Africa, Asia, and the Caribbean, many hundreds of whom will die unnecessarily in the course of this unethical, exploitative research."¹²⁰

The executive editor of the *New England Journal of Medicine* asserted that the studies violated the principles articulated in the Declaration of Helsinki, which requires that control groups receive the best proven therapy and makes no exception for instances in which that treatment is not locally available.¹²¹ More specifically, she argued: "The shift in wording between 'best' and 'local' may be slight, but the implications are profound. Acceptance of this ethical relativism could result in widespread exploitation of vulnerable Third World populations for research programs that could not be carried out in the sponsoring country."¹²²

114. George J. Annas & Michael A. Grodin, *Human Rights and Maternal-Fetal HIV Transmission Prevention Trials in Africa*, 88 AM. J. PUB. HEALTH 560, 561 (1998); see also Wechsler, *supra* note 70, at 29.

115. Bayer, *supra* note 103, at 570; see also Robert J. Levine, *The Need to Revise the Declaration of Helsinki*, 341 NEW ENG. J. MED. 531, 534 (1999).

116. See Karim, *supra* note 111, at 565.

117. See *id.* at 564.

118. *Id.*

119. Bayer, *supra* note 103, at 570.

120. *Id.* at 568 (citing P. Lurie et al., written communication, April 22, 1997).

121. See Marcia Angell, *The Ethics of Clinical Research in the Third World*, 337 NEW ENG. J. MED. 847, 847-48 (1997).

122. *Id.* at 848. A full analysis of the problems of biomedical research in developing countries is beyond the scope of this paper. Nonetheless, a few general recommendations concerning such research will be suggested in Part VI.B of this Article.

E. *Do the Risks Justify a Ban on Placebo Controls?*

Placebo controls can pose significant risks for human subjects who forego otherwise available treatment. The question remains, however, should placebo controls be banned from biomedical research in all circumstances in which standard therapy is available for patients?

The answer to this question is no. As discussed above, there are compelling scientific justifications for the inclusion of placebo controls in carefully designed clinical trials. Placebo-controlled trials can be more efficient, financially feasible, and informative than other types of studies. Several prominent commentators, including Professors Baruch Brody and Robert Levine, have likewise recognized that absolutist positions regarding placebo usage are inappropriate.¹²³

Levine states that available empirical evidence reveals that the role of research subjects participating in clinical trials, including those that are placebo-controlled, is generally not hazardous.¹²⁴ This evidence provides further support for the proposition that it is unnecessary to ban the use of placebo controls out of fear that they will commonly lead to human suffering and loss of life.

One study of 805 protocols involving 29,162 prisoner subjects during 614,534 days found only 58 adverse drug reactions that, with one exception, did not lead to death or permanent disability, though the one subject who did die was receiving a placebo.¹²⁵ Another review of 157 protocols involving 8,201 subjects identified only three "adverse effects" consisting of two headaches following spinal taps and a pneumonia that may have been unrelated to the study.¹²⁶ A third survey of 306,000 subjects over a period of eight years reported only thirteen insurance claims, seven of which resulted in an award of \$54 or less, four of which yielded an award of \$410 or more, and the largest of which led to a recovery of \$1,550.¹²⁷

123. Professor Baruch Brody states in his book, *Ethical Issues in Drug Testing, Approval, and Pricing*: "I neither approve nor disapprove of all placebo-controlled trials; some are acceptable and others are not." BRODY, *supra* note 57, at 125. Similarly, Professor Robert Levine states in *The Ethics and Regulation of Clinical Research*:

I have no position on the RCT [randomized clinical trial]. I can develop positions on particular RCTs, but in order to do this, I almost always require advice from various experts. . . .

At the time of this writing, the RCT is the *gold standard* for evaluating therapeutic efficacy. ROBERT J. LEVINE, *THE ETHICS AND REGULATION OF CLINICAL RESEARCH* 211 (1988). Levine discusses both placebo-controlled and active-controlled randomized clinical trials in his book.

124. LEVINE, *supra* note 123, at 40.

125. *Id.* at 39 (citing C.J.D. Zarafonitis et al., *Clinically Significant Adverse Effects in a Phase I Testing Program*, 24 *CLINICAL PHARMACOLOGY THERAPEUTICS* 127, 127-32 (1978)).

126. *Id.* at 40 (citing H. Bostrom, *On the Compensation for Injured Research Subjects in Sweden*, in *PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BIOMEDICAL AND BEHAVIORAL RESEARCH: COMPENSATING FOR RESEARCH INJURIES: THE ETHICAL AND LEGAL IMPLICATIONS OF PROGRAMS TO REDRESS INJURED SUBJECTS* 309-22 (App. 1982)).

127. *Id.* (citing D.J. McCann and R.J. Pettit, *A Report on Adverse Effects Insurance for Human Subjects*, in *PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND*

One commentator estimated that the risks of physical or psychological harm to clinical trial participants were slightly greater than those to which office secretaries are exposed, one-seventh as significant as those faced by window washers, and one-ninth as severe as the risks that confront miners.¹²⁸

Levine concludes that "arguments for policies designed to restrict research generally because it is hazardous are without warrant,"¹²⁹ though he does not suggest that research is so safe that there is no need to place any limits on biomedical studies.¹³⁰ It follows that, although placebo controls should not be utilized indiscriminately, they also should not be universally banned from clinical research.

The challenge is to determine when the use of placebo controls in biomedical studies is appropriate. For guidance one should look first to the federal regulations that govern clinical trials.

III. FEDERAL REGULATIONS GOVERNING THE USE OF PLACEBOS IN CLINICAL TRIALS

In order to analyze all of the issues relevant to the use of placebo controls, one must understand the general regulatory framework. Consequently, a somewhat detailed description of the federal oversight mechanisms for clinical research follows.

Research studies for drugs and devices, generally termed "clinical trials," are regulated by the FDA.¹³¹ Clinical trials for other therapies such as surgery or bone marrow transplants are not regulated by the FDA and are subject to DHHS regulation only if they are "conducted, supported or otherwise subject to regulation by any federal department or agency."¹³² Drugs studied in clinical trials are called investigational new drugs ("IND").¹³³ Sponsors wishing to conduct a clinical trial to test a new drug

BIOMEDICAL AND BEHAVIORAL RESEARCH: COMPENSATING FOR RESEARCH INJURIES: THE ETHICAL AND LEGAL IMPLICATIONS OF PROGRAMS TO REDRESS INJURED SUBJECTS 241-74 (App. 1982)).

128. *Id.* at 39 (citing J.D. Arnold, *Alternatives to the Use of Prisoners in Research in the United States*, in THE NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH: RESEARCH INVOLVING PRISONERS: REPORT AND RECOMMENDATIONS app. 8.1-8.18 (1976)).

129. *Id.* at 40.

130. *Id.*

131. See 21 C.F.R. § 7.3(f) (1999) (stating that "[p]roduct' means an article subject to the jurisdiction of the Food and Drug Administration, including any food, drug, and device intended for human or animal use").

132. 45 C.F.R. § 46.101(a) (1998); see also Norman Daniels & James E. Sabin, *Last Chance Therapies and Managed Care: Pluralism, Fair Procedures, and Legitimacy*, 1998 HASTINGS CENTER REP. 29; Richard S. Saver, Note, *Reimbursing New Technologies: Why Are the Courts Judging Experimental Medicine?*, 44 STAN. L. REV. 1095, 1110-11 (1992).

133. 21 C.F.R. § 312.23(a) (1999). Medical research for drugs is conducted in three or four phases of clinical trials. In Phase I, the new drug or treatment is given to patients or healthy individuals to

must submit IND applications to the FDA.¹³⁴

Research that is conducted, supported, or regulated by DHHS, the FDA, or another federal agency must be reviewed by an Institutional Review Board ("IRB").¹³⁵ An IRB is a committee designated by an institution to review, approve, and periodically monitor biomedical research studies.¹³⁶ Its principal purpose is to protect the rights and welfare of human subjects.¹³⁷ The IRB receives a document known as the "protocol" regarding each clinical trial that describes eligibility requirements for participants, the number of subjects to be tested, and the objective of the research.¹³⁸ The material submitted to the IRB also includes a document known as the "informed consent" form that will be provided to participants.¹³⁹ The document contains a detailed explanation of the clinical trial and is signed by the enrollee to indicate agreement to participate in the study. It is the duty of the IRB reviewing the research protocol to ensure that informed consent is sought from each research subject.¹⁴⁰

Both IRBs and the contents of informed consent forms are subject to extensive regulation by DHHS and the FDA. Each IRB must have at least five members with varying backgrounds and diversity in terms of race,

determine its toxicity, most effective method of administration, and safe dosage range. Participants in the trial receive increasing dosages of the substance in order to determine its metabolism, absorption, and side effects and to gain early evidence of its effectiveness, if possible. Phase I clinical trials generally involve only twenty to eighty subjects, last about a year, and have a very high failure rate. Seventy percent of drugs submitted for Phase I clinical trials fail to progress to Phase II.

Phase II trials are designed to determine the effectiveness of the therapy. The treatment is administered to patients afflicted with the disease for which the therapy is intended, and the trial often involves 100 to 300 people and lasts about two years. Approximately 33% of drugs submitted for clinical trials fail in Phase II testing.

Phase III clinical trials are conducted only after the treatment has proven effective through Phase I and II trials. The third phase attempts to assess the medical results of the experimental therapy in comparison with standard therapy or no therapy at all. Thus, it is in Phase III trials that placebos are often used. Phase III studies usually involve several hundred to several thousand patients and last about three years.

The FDA may also require postmarketing or Phase IV clinical trials. These studies are designed to determine the existence of less common adverse reactions, the effect of the drug on morbidity or mortality, or the effect of the drug on a particular patient population, such as children. See 21 C.F.R. §§ 312.21, 312.85 (1999); see also Veronica Henry, *Problems with Pharmaceutical Regulation in the United States*, 14 J. LEGAL MED. 617, 621-22 (1993).

134. 21 C.F.R. § 312.23(a) (2000). In some circumstances, a drug still under investigation may be used to treat patients not participating in a clinical trial. Specifically, an IND may be used in treatment of patients if the drug is intended to treat a serious or immediately life-threatening disease, and there is no comparable or satisfactory alternative drug or therapy. The drug can be used in treatment if it is currently under investigation in a clinical trial, or if clinical trials have been completed and the sponsor is actively pursuing marketing approval with due diligence. See 21 C.F.R. §§ 312.34(a)-(b) (2000).

135. 21 C.F.R. §§ 56.101, 56.103 (2000); 45 C.F.R. § 46.101(a) (1999).

136. 21 C.F.R. § 56.102(g) (2000); 45 C.F.R. § 46.102(g) (1999).

137. 21 C.F.R. § 56.102(g) (2000).

138. See 21 C.F.R. § 56.115 (2000); 45 C.F.R. § 46.115 (1999).

139. 21 C.F.R. § 50.20 (2000); 45 C.F.R. § 46.116 (1999).

140. See 21 C.F.R. § 56.111(a)(4) (2000); 45 C.F.R. § 46.111(a)(4) (1999).

gender, and culture.¹⁴¹ Each IRB must include at least one member whose principal concerns are in the scientific realm and one individual whose primary concerns are nonscientific (e.g., a lawyer or minister).¹⁴² Furthermore, each IRB must include at least one member who is not otherwise affiliated with the institution and who has no immediate family member affiliated with the research facility.¹⁴³

Unless an expedited review is necessary, research protocols must be reviewed at meetings at which a majority of the members of the IRB are present, including at least one member whose professional expertise is nonscientific.¹⁴⁴ A majority of the members present must vote for the approval of the research before the investigator can proceed with the study.¹⁴⁵

An IRB has authority to approve, disapprove, or require modifications to the research activities reviewed by it.¹⁴⁶ The IRB must provide written notification of its decision to those who proposed the research and is required to conduct continuing review of previously approved research at intervals of at least once a year, or more often, if the risks entailed necessitate more frequent assessment.¹⁴⁷

In order to approve proposed research, an IRB must ensure that specific criteria are met. These include: (1) risks to participants are minimized; (2) risks to subjects are reasonable in light of anticipated benefits; and (3) selection of participants is equitable, and the protocol is sensitive to the particularized problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled individuals, or economically or educationally deprived persons.¹⁴⁸

The information provided to participants on the informed consent document must be written in language that is comprehensible to the subject.¹⁴⁹ Informed consent may not include language that waives or appears to waive any of the subject's rights or releases the institution or personnel involved in the research from liability for negligence.¹⁵⁰ The regulations further require that informed consent be obtained in writing from each participant, though certain exceptions are allowed.¹⁵¹

The regulations detail the data that must be featured on the informed

141. 21 C.F.R. § 56.107(a) (2000); 45 C.F.R. § 46.107(a) (1999).

142. 21 C.F.R. § 56.107(c) (2000); 45 C.F.R. § 46.107(c) (1999).

143. 21 C.F.R. § 56.107(d) (2000); 45 C.F.R. § 46.107(d) (1999).

144. 21 C.F.R. § 56.108(c) (2000); 45 C.F.R. § 46.108(b) (1999).

145. 21 C.F.R. § 56.108(c) (2000); 45 C.F.R. § 46.108(b) (1999).

146. 21 C.F.R. § 56.109(a) (2000); 45 C.F.R. § 46.109(a) (1999).

147. 21 C.F.R. §§ 56.109(e)–(f) (2000); 45 C.F.R. §§ 46.109(d)–(e) (1999). As discussed in Part V.C.2, *infra*, IRBs have been harshly criticized for failing to conduct effective continuing reviews. They have been faulted for relying only on paperwork submitted by the investigators without conducting visits to research sites, interviewing subjects, and implementing other oversight mechanisms.

148. 21 C.F.R. § 56.111(a) (2000); 45 C.F.R. § 46.111(a) (1999).

149. 21 C.F.R. § 50.20 (2000); 45 C.F.R. § 46.116 (1999).

150. 21 C.F.R. § 50.20 (2000); 45 C.F.R. § 46.116 (1999).

151. 21 C.F.R. § 50.27 (2000); 45 C.F.R. § 46.117 (1999).

consent documentation. This information includes a description of the research, an explanation of its risks, benefits, and alternatives, a discussion of confidentiality, a list of contact people, and a statement that participation is voluntary and may be discontinued at any time.¹⁵²

The FDA will refuse to approve an application for a new drug if clinical tests show that it is unsafe or if insufficient information exists to determine whether it is safe.¹⁵³ A new drug cannot be introduced into interstate commerce unless it has been approved by the FDA.¹⁵⁴ Any person who introduces into commerce a new drug that has not been approved by the FDA can be imprisoned for up to a year and/or fined up to \$1,000, or if the

152. 21 C.F.R. §§ 50.25(a)–(b) (2000); 45 C.F.R. §§ 46.116(a)–(b) (1999). The provisions read as follows:

- (a) Basic elements of informed consent. . . . [I]n seeking informed consent the following information shall be provided to each subject:
 - (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
 - (2) A description of any reasonably foreseeable risks or discomforts to the subject;
 - (3) A description of any benefits to the subject or to others which may reasonably be expected from the research;
 - (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
 - (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
 - (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained;
 - (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
 - (8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- (b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:
 - (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
 - (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
 - (3) Any additional costs to the subject that may result from participation in the research;
 - (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
 - (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and
 - (6) The approximate number of subjects involved in the study.

45 C.F.R. §§ 46.116(a)–(b) (1999).

153. 21 C.F.R. §§ 314.125(b)(3)–(4) (2000); 21 U.S.C. § 355(d) (1994).

154. 21 U.S.C. § 355(a) (1994).

violation is committed "with the intent to defraud or mislead," the fine is increased to \$10,000, and imprisonment can be for up to three years.¹⁵⁵

As described previously, the FDA outlines five different design options for drug studies. Investigators may utilize a variety of controls in their clinical trials, including placebo controls, dose-comparison controls, no-treatment controls, active treatment controls, and historical controls.¹⁵⁶

The FDA regulations provide only limited guidelines as to when any one of the five study designs should be selected. The FDA recommends the use of active controls in circumstances in which "administration of placebo or no treatment would be contrary to the interest of the patient."¹⁵⁷ However, it fails to offer any further guidance as to when the welfare of the patient would necessitate the use of a standard therapy control. There have been no published cases in which patients have sued investigators for the inappropriate use of a placebo control in a clinical trial. Consequently, caselaw also provides no guidance as to this issue.

In order to evaluate when, if ever, the use of placebo controls is appropriate, one must be familiar not only with federal regulations, but also with

155. 21 U.S.C. §§ 333(a)(1)-(2) (1994); *see also* United States v. Najarian, 915 F. Supp. 1460, 1460 (D. Minn. 1996). The defendant was prosecuted for failure to comply with FDA regulations governing experimental drug programs.

156. 21 C.F.R. § 314.126(b)(2) (2000). The provision reads:

(i) *Placebo concurrent control.* The test drug is compared with an inactive preparation designed to resemble the test drug as far as possible. A placebo-controlled study may include additional treatment groups, such as an active treatment control or a dose-comparison control, and usually includes randomization and blinding of patients or investigators, or both.

(ii) *Dose-comparison concurrent control.* At least two doses of the drug are compared. A dose-comparison study may include additional treatment groups, such as placebo control or active control. Dose-comparison trials usually include randomization and blinding of patients or investigators, or both.

(iii) *No treatment concurrent control.* Where objective measurements of effectiveness are available and placebo effect is negligible, the test drug is compared with no treatment. No treatment concurrent control trials usually include randomization.

(iv) *Active treatment concurrent control.* The test drug is compared with known effective therapy; for example, where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient. An active treatment study may include additional treatment groups, however, such as a placebo control or a dose-comparison control. Active treatment trials usually include randomization and blinding of patients or investigators, or both. If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.

(v) *Historical control.* The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self evident (general anesthetics, drug metabolism).

157. 21 C.F.R. § 314.126(b)(2)(iv) (2000).

general principles of research ethics. Several doctrines have been developed by various national and international bodies in an effort to identify the ethical principles that should govern biomedical research involving human subjects. While these doctrines provide important guidance for clinical investigators, their value is limited.

IV. STATUS OF PLACEBOS UNDER ETHICAL GUIDELINES

Ethical guidance relevant to the use of placebos in clinical trials can be found in three primary sources: the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report. A brief overview of each is provided in this section.

A. *The Nuremberg Code*

The most notorious large-scale medical experimentation in human history was conducted by the Nazis during World War II. The elite of the German medical community subjected innocent victims in concentration camps to "a broad range of 'ghastly' and 'hideous'" experimentation.¹⁵⁸ In Buchenwald and Natzweiler, numerous healthy inmates were involuntarily infected with yellow fever, smallpox, typhus, cholera, and diphtheria germs, as a consequence of which hundreds of them died.¹⁵⁹ In other camps Nazi doctors conducted experiments relating to high altitude, malaria, freezing, mustard gas, bone transplantation, sea water, sterilization, and incendiary bombs.¹⁶⁰

The full extent and inhumanity of the medical experimentation conducted by Nazi doctors in concentration camps became public knowledge during the Nuremberg Trials after World War II.¹⁶¹ As a result of the Nuremberg Trials, the Nuremberg Code was promulgated.¹⁶² The Code is included in the Nuremberg Military Tribunal's decision in the case of *United States v. Brandt*.¹⁶³ The Code features ten points that delineate the circumstances under which medical experimentation on human subjects is permissible.¹⁶⁴ The Code emphasizes the need for informed consent and minimi-

158. ALLEN M. HORNBLUM, *ACRES OF SKIN* 75 (1998).

159. *Id.*

160. *Id.* at 75, 77.

161. Colleen M. McCarthy, *Experimentation on Prisoners: The Inadequacy of Voluntary Consent*, 15 NEW ENG. J. ON CRIM. & CIV. CONFINEMENT 55, 57 (1989). The Nuremberg Trials were opened on November 20, 1945 at the Palace of Justice in Nuremberg, Germany. Twenty-one Nazi physicians were found guilty of "war crimes and crimes against humanity," and seven of them were sentenced to death. Bernard Meltzer, "War Crimes": *The Nuremberg Trial and the Tribunal for the Former Yugoslavia*, 30 VAL. U. L. REV. 895, 896 (1996); see also McCarthy, *supra*, at 57 n.10 (counting twenty-three defendants).

162. McCarthy, *supra* note 161, at 57.

163. REICH, *supra* note 9, at vol. 5, app. 2763.

164. NUREMBERG CODE, *supra* note 20, at 181-82. The full text of the Nuremberg Code is as follows:

zation of risk to the subject and provides that clinical studies must be designed to "avoid all unnecessary physical and mental suffering and injury."¹⁶⁵ It makes no specific mention, however, of placebos or placebo controls.

B. *The Belmont Report*

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was created by the National Research Act of 1974¹⁶⁶ and operated between 1974 and 1978.¹⁶⁷ One of the Commission's tasks was to identify the basic ethical principles that govern clinical studies involving human subjects.¹⁶⁸ The Commission began its

1. 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, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved 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.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where 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.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

165. *Id.* at 182.

166. National Research Act of 1974, Pub. L. No. 93-348, § 201, 88 Stat. 342, 348.

167. BRODY, *supra* note 57, at 103.

168. National Research Act of 1974, Pub. L. No. 93-348, § 202(1), 88 Stat. 342, 349.

effort to identify those principles at a conference held in 1976 at the Belmont Conference Center of the Smithsonian Institution.¹⁶⁹ It ultimately published its conclusions in 1979 in the Belmont Report, which is recognized as an important exposition of research ethics.¹⁷⁰

The Belmont Report identifies three basic ethical principles: (1) respect for persons; (2) beneficence; and (3) justice.¹⁷¹ Respect for persons requires "that individuals should be treated as autonomous agents" and "that persons with diminished autonomy are entitled to protection."¹⁷² This principle thus requires both an acknowledgement of personal autonomy and protection of those who are vulnerable because of diminished capacity.¹⁷³

Beneficence is defined as a two-fold obligation on the part of researchers. First, investigators must "do no harm" to study participants, and second, they must "maximize possible benefits and minimize possible harms" to human subjects.¹⁷⁴

The concept of justice focuses on the question of "[w]ho ought to receive the benefits of research and bear its burdens."¹⁷⁵ Justice requires fairness of distribution of the burdens and benefits of scientific research.¹⁷⁶

In a separate section, entitled "Applications," the Belmont Report describes the applications of the three ethical principles upon which it focuses. In practical terms, respect for persons demands that investigators obtain informed and voluntary consent from all human subjects.¹⁷⁷ Beneficence requires a careful assessment of the risks and benefits of a clinical trial to determine whether the study is properly designed and whether the risks that it will pose for participants are justified.¹⁷⁸ The Belmont Report addresses justice at two levels: individual and social.¹⁷⁹ To achieve justice at the individual level, investigators must assure a fair selection of human subjects.¹⁸⁰ Social justice considerations compel the protection of vulnerable populations such as children, prisoners, and the "mentally infirm."¹⁸¹

The Belmont Report does not indicate which, if any, of the three ethical principles is of most importance and how they are to be prioritized if a

169. BRODY, *supra* note 57, at 103.

170. See Belmont Report, *supra* note 14, at 23, 192.

171. *Id.* at 23, 193-94.

172. *Id.* at 23, 193.

173. *Id.* at 23, 194. The principle of justice similarly requires protection of vulnerable subjects. See *id.* at 23, 197.

174. *Id.* at 23, 194.

175. *Id.*

176. *Id.*

177. *Id.* at 23, 195.

178. *Id.* at 23, 195-96.

179. *Id.* at 23, 196.

180. *Id.*

181. *Id.*

conflict exists among them.¹⁸² Some scholars have argued that respect for persons and their right of autonomy and self-determination should supersede other values in cases of conflict.¹⁸³ Others have advocated a more balanced approach, viewing the need to develop beneficial treatments through biomedical research as outweighing autonomy in particular circumstances.¹⁸⁴

C. *The Declaration of Helsinki*

The Declaration of Helsinki, which outlines recommendations for biomedical research involving human subjects, was adopted by the Eighteenth World Medical Association General Assembly at Helsinki, Finland in 1964.¹⁸⁵ The Declaration has subsequently been revised again in 1975, 1983, 1989, 1996, and 2000.¹⁸⁶

The Declaration of Helsinki provides the following: "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists."¹⁸⁷ The Declaration of Helsinki thus instructs that the use of placebos in medical research is always unethical if treatment is available for the condition in question. This language was adopted in the most recent revision of the document at the Fifty-Second World Medical Association General Assembly in 2000.¹⁸⁸

182. Harold Y. Vanderpool, *Introduction to Part I*, in *THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS: FACING THE 21ST CENTURY* 34 (Harold Y. Vanderpool ed., 1996).

183. See Robert M. Veatch, *From Nuremberg Through the 1990s: The Priority of Autonomy*, in *THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS: FACING THE 21ST CENTURY*, *supra* note 182, at 46-57; see also Jay Katz, *Human Experimentation and Human Rights*, 38 ST. LOUIS U. L.J. 7 (1993).

184. See Albert R. Jonsen, *The Weight and Weighing of Ethical Principles*, in *THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS: FACING THE 21ST CENTURY*, *supra* note 182, at 59-81; see also Terrence F. Ackerman, *Choosing Between Nuremberg and the National Commission: The Balancing of Moral Principles in Clinical Research*, in *THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS: FACING THE 21ST CENTURY*, *supra* note 182, at 83-101.

185. *DECLARATION OF HELSINKI*, *supra* note 21.

186. *Id.*

187. *Id.* ¶ C.29.

188. *Id.* Prior to its 2000 revision, the Declaration of Helsinki stated 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." WORLD MED. ASS'N, *DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS* ¶ II.3. (amended 1996). This statement was also interpreted as prohibiting the use of a placebo control whenever a proven treatment existed for the condition under study. Rothman & Michaels, *supra* note 23, at 394. One critic, however, pointed out that a literal reading of this principle would render all biomedical research unethical, since the experimental treatment being tested in any clinical trial is by definition unproven. Nightingale, *supra* note 13, at 498. Even in trials that include an active control, any subject who receives the intervention under study rather than standard therapy in the control group is receiving an intervention that is not the "best proven" treatment, since, as an experimental therapy, it is necessarily unproven. *Id.* The Declaration was revised in response to criticism regarding its lack of clarity and as a reaction against the pla-

The Declaration of Helsinki establishes a restrictive and inflexible rule. The standard has been criticized for its rigidity by DHHS's Office for Human Research Protection and is highly unlikely to be incorporated into the federal regulations.¹⁸⁹ The Nuremberg Code and the Belmont Report, like the federal regulations, provide no definitive guidelines for those conducting placebo-controlled clinical trials. Thus, a pressing need remains for meaningful guidance that is sensitive to the needs of both researchers and human subjects.

V. THE CHALLENGES OF FORMULATING ETHICAL GUIDELINES

Placebo controls can offer significant scientific benefits and are often chosen by investigators because of their efficiency. In formulating research policies, however, regulators cannot focus solely on the efficiency of a particular research tool. Ethical standards must be anchored in broader principles that address the rights of human subjects and the duties of medical professionals. The challenge of developing effective guidance is complicated by the tensions and ambiguities inherent in the ethical principles of beneficence and autonomy. Guidance must also take into account certain realities relating to the complex role of the investigator and the limitations of IRB oversight. The concepts of beneficence and autonomy and the functions of researchers and IRBs will be analyzed in this section.

A. *Beneficence as a Guiding Principle*

Beneficence requires that researchers "do no harm" to study participants and that they "maximize possible benefits and minimize possible harms" to human subjects.¹⁹⁰ Many patients assume that for doctors, the welfare of the patient is always, without question, primary. In the research context, however, this assumption is somewhat naïve. Those designing placebo-controlled clinical studies must grapple with the sometimes competing demands of beneficence and rigorous scientific inquiry.

As noted above, in some cases, patients who take placebos derive a direct benefit as their symptoms improve or disappear as a result of the pla-

cebo-controlled trials that were conducted in developing countries to test new protocols to prevent mother-to-child HIV transmission. See *supra* part II.D.2; Susan Okie, *Health Officials Debate Ethics of Placebo Use*, WASH. POST., Nov. 24, 2000, at A3.

189. David Brown, *Medical Research Group Revises Guidelines on Placebos*, WASH. POST, Oct. 8, 2000, at A2 (quoting Greg Koski, Director of the Office for Human Research Protection, as stating that "it would be a mistake to rule out the use of placebos in well-designed research" and that he did not believe the revised standard would serve "as the literal basis for new regulations"). The article further notes that "[t]aken literally, the new language would push hundreds, if not thousands, of clinical trials here and abroad beyond the boundaries of ethical acceptability." *Id.* See also Okie, *supra* note 188 (discussing criticisms of the revised Declaration of Helsinki).

190. Belmont Report, *supra* note 14, at 23, 193-23, 194.

cebo effect.¹⁹¹ In drug trials, administering placebos to such patients is fully consistent with the principle of beneficence. The subjects profit from the study and are placed at no risk because they receive only an inactive agent. In the case of sham surgeries, the practice is more dubious because the patients are exposed to the risks of anesthesia and an incision. However, when patients improve after sham surgery, the procedure can be deemed beneficent since the subjects benefit from the medical attention they received.

The ethical question is more complicated when patients are likely to experience no benefit from taking a placebo or may even deteriorate as a result of being deprived of active therapy. Then one must ask whether the benefit that will potentially be gained in the future from the research results justifies the immediate harm to the individual study participant. Unfortunately, it is impossible to predict whether any subjects in a given clinical trial will experience improvement with placebos. Consequently, applicable guidelines should not assume a direct benefit to participants from the placebo effect or rely on the placebo effect as a justification for placebo use in clinical trials.

1. *Kant's Categorical Imperative*

A possible response to the question of when placebo usage is appropriate is suggested by Immanuel Kant's categorical imperative, which requires that human beings always be treated as ends in themselves and not merely as a means to another's ends.¹⁹² Kant could, therefore, argue that researchers should never expose an individual to risk for the purpose of finding a cure for future patients when the individual subject stands to gain no benefit from the experiment and will serve only as a means to scientific inquiry. He might oppose the utilization of placebos in clinical research based exclusively on their efficiency since such use arguably disregards human subjects as ends in themselves.

Biomedical research, however, constitutes a difficult context in which to apply the categorical imperative because of research's many complexities and ambiguities. Kant, likely, would not support the cessation of all clinical research since in its absence new treatments cannot be developed. Yet, interpreted literally, his categorical imperative could stand for such a proposition. Those who receive experimental treatments in clinical trials are always utilized as a means to an end, because the effectiveness and safety of the treatment being tested is unknown and the substance may cause significant harm to subjects.¹⁹³ By contrast, those who receive pla-

191. See *supra* Part II.B.

192. See IMMANUEL KANT, FOUNDATIONS OF THE METAPHYSICS OF MORALS 54-55 (Lewis White Beck trans., 2d ed., MacMillan Publ'g Co. 1990) (1785).

193. In recent years, for example, High Dose Chemotherapy with Autologous Bone Marrow Transplantation ("HDC-ABMT") for breast cancer patients has generated considerable controversy. While

cebos in clinical drug studies avoid exposure to the potential hazards of the therapy being tested although they might receive no benefit from the inactive agent.

Nevertheless, if the trial proves the experimental treatment to be safe and effective, participants in all of the study arms have much to gain. Those who have taken the new drug during the study will have already benefited from it, and those in the placebo group will be able to receive the new medication once it is approved by the FDA, or, in some circumstances, even before formal approval is granted.¹⁹⁴ If placebo controls allow the study to be completed quickly and efficiently, participants in the control arm will gain access to the new drug that much faster.

Furthermore, placebos might be essential to the viability of the biomedical study. In some instances, utilization of an active control might be so expensive that it would render the research project financially unfeasible. Thus, if barred from using placebos, investigators would abandon their effort to develop improved treatment for the condition in question. All of these factors make it difficult to apply Kantian theory to clinical research and obfuscate the issue of whether subjects in either arm of a clinical trial serve as a means to an end or an end in themselves.

2. *Beneficence Does Not Preclude Utilitarian Considerations*

Utilitarian theory, initially developed by Jeremy Bentham and John Stuart Mill, teaches that choices should be made based on the amount of happiness that they produce.¹⁹⁵ Given alternatives, one should always select the course of action that promotes the greatest happiness.¹⁹⁶ The primary utilitarian value is the common good, defined as the greatest happiness for the greatest number of people.¹⁹⁷ Thus, the welfare of particular individuals theoretically may be compromised for the sake of a sufficiently

many patients have been eager to receive HDC-ABMT as a last-chance therapy, four out of five international clinical trials involving over 2000 women found "no significant difference in survival between patients receiving [HDC-ABMT] and those receiving lower-dose chemotherapy without transplant support." Stephanie Stapleton, *Early Results Question Benefit of High-dose Chemotherapy*, AM. MED. NEWS, May 10, 1999, at 29. The results of the fifth trial, conducted in South Africa, were ultimately discredited since the investigator was found to have falsified his data. Denise Grady, *Breast Cancer Researcher Admits Falsifying Data*, N.Y. TIMES, Feb. 5, 2000, at A9. Moreover, according to experts, between 5 and 20% of patients who undergo HDC-ABMT die from the procedure rather than from the underlying disease. The experimental procedure, therefore, may be more dangerous for patients than it is beneficial. See Jennifer L. Hardester, Note, *In Furtherance of an Equitable, Consistent Structure for Reviewing Experimental Coverage Decisions: The Lessons of Pitman v. Blue Cross and Blue Shield of Oklahoma*, 14 ST. LOUIS U. PUB. L. REV. 289, 294 (1994).

194. An IND may be used in treatment of patients if the drug is intended to treat a serious or immediately life threatening disease, there is no comparable or satisfactory alternative drug or therapy, and the sponsor is actively pursuing marketing approval with due diligence. 21 C.F.R. § 312.34(b) (2000).

195. BARRY R. FURROW ET AL., BIOETHICS: HEALTH CARE LAW AND ETHICS 7 (3d ed. 1997).

196. See *id.*

197. See *id.*

significant benefit to the community.¹⁹⁸

The ethical doctrines that govern biomedical research do not reject utilitarian values. The Nuremberg Code, for example, instructs that "[t]he experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature."¹⁹⁹ It thus does not focus exclusively on individual rights and ignore societal welfare. The Code asserts that experiments should not be conducted if researchers have "an *a priori* reason to believe that death or disabling injury will occur,"²⁰⁰ but does not prohibit investigators from exposing subjects to some risk, with their consent, if society stands to gain substantial benefit. Rather, according to the Nuremberg Code, clinical studies must be designed so that the degree of risk never exceeds "that determined by the humanitarian importance of the problem to be solved by the experiment."²⁰¹

When placebo controls significantly enhance the accuracy of study results without causing participants to suffer death or disability, their utilization would comply with the mandates of the Nuremberg Code. While the Code outlines numerous safeguards that should be implemented to protect human subjects, it does not promote a ban on placebo controls and recognizes the importance of designing studies in a manner that will produce useful results.

The value of utility is also consistent with the concept of beneficence, as described in the Belmont Report. Beneficence requires a systematic assessment of the risks and benefits of research, which should be shown to be "in a favorable ratio."²⁰² Beneficence does not require the elimination of all risks to study subjects. The Belmont Report instructs that "[r]isks should be reduced to those necessary to achieve the research objectives."²⁰³ Furthermore, "[r]isk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures."²⁰⁴ The Belmont Report therefore recognizes that researchers might need to expose consenting participants to minimal risks in the course of a study in order to obtain accurate and useful results.²⁰⁵

Beneficence encompasses not only concern for the individual research subject, but also consideration of the welfare of society at large. Some risks to individual participants might be justified by the long-term benefits

198. See *id.*; Thomas Morawetz, *Persons Without History: Liberal Theory and Human Experience*, B.U. L. REV. 1013, 1018 (1986).

199. NUREMBERG CODE, *supra* note 20, at 182.

200. *Id.*

201. *Id.*

202. Belmont Report, *supra* note 14, at 23, 196.

203. *Id.*

204. *Id.*

205. See *id.*

to society stemming from the "improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures."²⁰⁶ Beneficence, at times, is therefore an ambiguous concept. It covers both individual and societal claims that "may come into conflict and force difficult choices."²⁰⁷

The Belmont Report provides no guidance as to how the conflict between individual benefit and societal good should be resolved. It does not rule out the possibility that at times societal demands will require that individual needs be compromised to some extent and that risk be accepted because of the efficiency of a particular research mechanism.

While the efficiency of placebos constitutes a compelling justification for their inclusion in clinical trials, that efficiency cannot be considered in isolation. Traditional utilitarianism has been criticized for ignoring the individual's own moral worth.²⁰⁸ Pure utilitarianism suggests that if enough happiness is achieved for others through violation of individual rights, including torture or death, such violations are morally appropriate or even necessary.²⁰⁹

Although beneficence does not preclude consideration of utilitarian benefits, it surely would not permit researchers to inflict extreme harm on individual subjects for the sake of the common good. To the contrary, beneficence requires that physicians "maximize possible benefits and minimize possible harms" to subjects.²¹⁰ The principle of beneficence, however, leaves open the question of where exactly the line should be drawn, that is, how much harm to subjects should be tolerated. For an answer to this inquiry one might turn to the concept of autonomy.

B. *Autonomy as a Guiding Principle*

Autonomy, like beneficence, is identified in the Belmont Report as an essential principle of biomedical ethics.²¹¹ One approach to determining when utilization of placebo controls is appropriate is to rely on the autonomy of subjects. According to this approach, so long as participants are fully informed about the details of the placebo-controlled clinical trial and make an autonomous decision to consent, the study should proceed without objection. In emphasizing the importance of informed consent, the federal regulations rely largely on autonomy as a safeguard for the welfare of human subjects.²¹² Like beneficence, however, the principle of autonomy is

206. *Id.* at 23,194.

207. *Id.*

208. See RONALD DWORKIN, *TAKING RIGHTS SERIOUSLY* 94-100 (1977); see also JOHN RAWLS, *A THEORY OF JUSTICE* 22-27 (1971).

209. See Joseph Mendola, *Hart, Fuller, Dworkin, and Fragile Norms*, 52 SMU L. REV. 111, 124 (1999).

210. Belmont Report, *supra* note 14, at 23,194.

211. *Id.* at 23,193.

212. See 21 C.F.R. § 50.25 (1999); 45 C.F.R. § 46.116 (1998).

at times ambiguous and provides incomplete guidance for medical researchers.

The Belmont Report mandates respect for persons and instructs that individuals "should be treated as autonomous agents."²¹³ The concept of autonomy is a philosophical ideal that is centuries old. Immanuel Kant viewed personal autonomy as the highest moral value and taught that all rational beings are endowed with free will.²¹⁴ According to Kant, "the concept of autonomy is inseparably connected with the Idea of freedom, and with the former there is inseparably bound the universal principle of morality, which is the ground in Idea of all actions of rational beings."²¹⁵

When considered in the context of biomedical research, autonomy would require that potential subjects be allowed to make independent decisions about participation in clinical studies.²¹⁶ Individuals should be given all of the information necessary to make an educated determination as to whether they wish to enroll in the trial.²¹⁷ They should not be pressured or swayed by investigators and should make their own assessments of the risks and benefits of participation.²¹⁸ If a fully informed person autonomously elects to participate in clinical research, the decision to do so is ethically valid.²¹⁹

Potential enrollees, as autonomous agents, arguably, should be free to decide whether to accept the risks posed by the clinical trial, no matter how significant they are. Some patients may be willing to forgo treatment for their own benefit out of a sense of altruism. They might wish to assist researchers in finding a cure even at the expense of their own health or at the cost of their lives.

The value of autonomy, however, does not support the indiscriminate use of placebos in clinical trials. For a variety of reasons, autonomy justifies the use of placebos only in a limited subset of research studies. Considerable evidence reveals that subjects are rarely, if ever, motivated by altruism, that the informed consent process is often flawed, and that serious illness severely diminishes patient autonomy and judgment. The patients who are sickest and have most to lose as a result of forgoing treatment in a placebo-controlled clinical trial are also the least able to make rational, responsible decisions. Consequently, the utilization of placebo controls should be limited to trials involving subjects who are not at risk of death,

213. Belmont Report, *supra* note 14, at 23,193.

214. See KANT, *supra* note 192, at 57-58, 63-70. Kant believed that free will and autonomy are the basis of the categorical imperative. Because individuals possess these qualities, they must be treated as ends rather than means. See *id.* at 71-73.

215. *Id.* at 70.

216. See Belmont Report, *supra* note 14, at 23,195.

217. See *id.*

218. See *id.*

219. See *id.*

permanent disability, or unbearable pain. In trials that do pose these risks for participants, researchers should not rely on subject autonomy as validating the use of placebo controls and should utilize active or historical controls instead.

1. *Altruism*

Professor Baruch Brody, a prominent scholar, focuses on altruism in making the following recommendation regarding the use of placebo controls:

[I]t is ethical to withhold from a control group a therapy that has not yet been formally approved but that has been shown in one or more trials to be effective and safe, even if the subjects in the placebo control group are thereby exposed to a greater risk of long-term losses, only if those losses and the probabilities of their occurring are sufficiently small that (1) the subject, informed of all of this, freely consents to being randomized into the trial and (2) reasonable people, of an average degree of altruism and risk-aversiveness, informed of all this, might consent to being randomized into the trial.²²⁰

Professor Brody is correct to conclude that placebo controls are permissible if the risks that they engender are relatively small. His solution, however, is imperfect. Professor Brody's formulation does not require physicians to eliminate as many risks as possible and to implement sufficient safeguards to ensure that the subject does not suffer long-term harm. Rather, an increased risk of long-term losses is acceptable so long as a person of average altruism and risk-aversiveness "might consent to being randomized into the trial."²²¹ This approach could lead to sloppy trial design and the incorporation of unnecessary risks on the assumption that a patient of "average altruism" might not find them objectionable.

Furthermore, it is impossible to determine what constitutes an "average degree of altruism." The standard is wholly subjective and cannot be proven empirically. Each investigator will perceive "average altruism" to exist at a different level, and thus every researcher would be free to incorporate a different amount of risk into his or her clinical trials. Finally, Professor Brody's proposed standard ignores important realities relating to the motivations of patients who enroll in biomedical research studies.

a. Subjects Do Not Enter Clinical Trials Because of Altruism

It is unrealistic to expect that most individuals enter clinical trials for

220. BRODY, *supra* note 57, at 124.

221. *Id.*

altruistic reasons.²²² A review of sixty-one studies on attitudes towards clinical trials, published in the *British Medical Journal*, found that "[a] large number of participants . . . emerge from consultations expecting to benefit personally; self interest, rather than altruism, seems to be their motive for participating."²²³ Furthermore, the review found that potential participants' willingness to be randomized diminished as they were given more preliminary data regarding the effectiveness of the experimental therapy.²²⁴ Those who were given less information and who were told that the outcome was "uncertain" were more willing to undergo randomization.²²⁵

A survey of twenty-seven cancer patients who agreed to participate in a Phase I trial revealed comparable findings.²²⁶ The results of the survey showed that patients were motivated primarily by the chance to benefit from the treatment.²²⁷ Although a minority of patients stated that they had altruistic motivations when they were asked specifically about their desire to help future cancer sufferers, none listed altruism in response to open-ended questions.²²⁸ The authors conclude that altruistic feelings play at most a limited role in motivating some patients to enroll in clinical trials.²²⁹

Other commentators have similarly found that subjects believe that they will benefit from participation in clinical trials even when they are clearly informed that there is a fifty-fifty chance that they will not receive active treatment.²³⁰ In one instance, participants in clinical trials indicated to interviewers that they trusted their doctors, believed that their physicians would do nothing to harm them, and were certain that the physician-researcher always acts in their best medical interest.²³¹ Patients in Phase I clinical oncology trials opted for participation based on hope of therapeutic benefit, despite the low likelihood of experiencing medical improvement

222. Some clinical trials involve healthy subjects who volunteer to undergo procedures or take medication that will clearly be of no therapeutic value to them. Many other trials involve patients who are recruited for studies that test therapies that may be useful in treating their conditions. Healthy volunteers might participate in clinical trials out of altruism, but they are often paid considerable sums of money for their enrollment, and these payments may constitute their true incentive. As discussed below, subjects who are also patients that are afflicted with the condition to be studied, are most often motivated by a desire to find effective treatment.

223. Sarah J.L. Edwards et al., *The Ethics of Randomised Controlled Trials from the Perspectives of Patients, the Public, and Healthcare Professionals*, 317 BRIT. MED. J. 1209, 1209 (1998).

224. *Id.* at 1209, 1211.

225. *Id.* at 1211.

226. See Christopher Daugherty et al., *Perceptions of Cancer Patients and Their Physicians Involved in Phase I Trials*, 13 J. CLINICAL ONCOLOGY 1062 (1995).

227. *Id.* at 1066.

228. *Id.*

229. *Id.*

230. See Ruth Macklin, *The Ethical Problems with Sham Surgery in Clinical Research*, 341 NEW ENG. J. MED. 992, 994 (1999).

231. *Id.*; ADVISORY COMM. ON HUMAN RADIATION EXPERIMENTS, FINAL REPORT OF THE ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS 484 (1996).

from treatment provided in Phase I studies.²³² In another instance, a study indicated that even after providing informed consent, six of fourteen adult subjects who received a placebo in a nonblind, nonrandomized placebo trial believed that their capsules contained an active medication,²³³ and three experienced side effects that they attributed to the pills.²³⁴

Parkinson's disease patients who underwent a sham surgery instead of receiving fetal tissue transplantation in a randomized study were told that they would be eligible for the real transplantation procedure if, at the conclusion of the trial, it was proven beneficial.²³⁵ Since the study revealed a higher than anticipated rate of adverse incidences, the participants in the control group were not offered the transplantation procedure.²³⁶ Several subjects were outraged and indicated that they would not have participated in the study if they had known that they would not immediately receive the real therapy at the conclusion of the study.²³⁷ A commentator cites the example of one woman: "[She] stated that she and her husband, who had participated in the study, felt they had been 'double shammed': first when they learned that her husband had undergone the sham procedure, and then when he was denied the real surgery on the basis of safety considerations."²³⁸

This evidence reveals that subjects most commonly enroll in clinical studies hoping to improve their own health, instead of hoping to further scientific inquiry or help others. Altruism is thus irrelevant to the calculus of many human subjects.

b. Soliciting Altruism From Subjects Is Inconsistent With Existing Ethical Guidelines

The ethical guidelines that govern human research emphasize the need to protect human subjects and to minimize the hazards of each study, re-

232. See ADVISORY COMM. ON HUMAN RADIATION EXPERIMENTS, *supra* note 231, at 484.

233. See Lee C. Park and Lino Covi, *Nonblind Placebo Trial: An Exploration of Neurotic Patients' Responses to Placebo When Its Inert Content Is Disclosed*, 12 ARCHIVES GEN. PSYCHIATRY 336, 339, 342 (1965). The subjects in this study were adult neurotic outpatients who were not alcoholic and had no neurological disorder. *Id.* at 336. Since the trial was nonblind and nonrandomized, those receiving the placebo were told that they were not being given an active agent. *Id.* at 337, 342.

234. *Id.* at 339, 342.

235. Macklin, *supra* note 230, at 994.

236. *Id.*

237. *Id.*

238. *Id.*; see also Paul S. Appelbaum et al., *False Hopes and Best Data: Consent to Research and the Therapeutic Misconception*, 17 HASTINGS CENTER REP. 20 (1987). The article examined informed consent procedures in research studies involving psychiatric illness. The authors found that despite very detailed explanations, 44% of participants in studies with a no-treatment or placebo control arm failed to realize that some enrollees who wished to receive treatment would not be given any. Thirty-two of eighty subjects stated that they believed the assignment would be made on the basis of their medical needs. In addition, "many of these subjects constructed elaborate but entirely fictional means by which an assignment would be made that was in their best interests." *Id.* at 21.

ardless of whether participants would be willing to accept greater risk. None of the guidelines discusses consideration of potential altruistic motives on the part of human subjects.

The Nuremberg Code, for example, instructs that "[t]he experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury."²³⁹ The Declaration of Helsinki directs that "[i]t is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject."²⁴⁰ This statement suggests that investigators should be guided by a paternalistic concern for subjects. They must focus upon eliminating as many risks as possible from their research studies and should not consider whether individuals might be willing to accept some risks for altruistic reasons. The physician's responsibility towards human subjects is never diminished by the patients' potentially noble motivations in selecting participation.

2. *The Informed Consent Process Is Often Severely Flawed*

An increasing volume of evidence indicates that the informed consent process is severely flawed in many cases. In consenting to enroll in clinical research, human subjects often do not exercise their autonomy in a meaningful way either because they are given insufficient information or because they do not comprehend the data they receive.

A 1998 statement issued by the DHHS's Office of Inspector General was highly critical of contemporary research oversight.²⁴¹ It noted that a 1995 Advisory Commission on Human Radiation Experiments interviewed actual research subjects and found that few realized they were participating in research and many did not understand the informed consent forms they signed.²⁴²

Numerous studies have shown that research subjects generally have difficulty providing ethically valid consent.²⁴³ In a labor-induction study of fifty-two women, 39% were found to be unaware that they were participating in a research study although all had signed informed consent forms.²⁴⁴ In addition, those who realized they were research subjects often misunder-

239. NUREMBERG CODE, *supra* note 20, at 182.

240. DECLARATION OF HELSINKI, *supra* note 21, ¶ B.10.

241. See *Protecting Human Clinical Research Patients Before the House Comm. on Gov't Reform & Oversight Subcomm. on Human Resources*, 105th Cong. (1998) (statement of George Grob, Deputy Inspector General for Evaluation and Inspections, Department of Health and Human Resources), available at 1998 WL 12761511 [hereinafter *Hearing*].

242. See *id.*

243. See Evan G. DeRenzo et al., *Assessment of Capacity to Give Consent to Research Participation: State-of-the-Art and Beyond*, 1 J. HEALTH CARE L. & POL'Y 66, 69 (1998).

244. Bradford H. Gray, *Complexities of Informed Consent*, 437 ANNALS AM. ACAD. POL. & SOC. SCI. 37, 43 (1978). Gray states that the women's misunderstanding is attributable to several factors "including the generally low educational levels of the unaware subjects, the investigator's delegation to subordinates of the task of obtaining consent, seeking consent in the labor room, and providing little oral explanation—'sign this and we can get started.'" *Id.*

stood essential aspects of the study and their role in it.²⁴⁵

Investigations regarding the decisional capacity of psychiatric research subjects have demonstrated that subjects were confused about the differences between research and clinical treatment.²⁴⁶ Subjects commonly were certain that their research participation would be of medical benefit to them, despite explanations to the contrary, a phenomenon known as "therapeutic misconception."²⁴⁷

Several researchers asked fifty oncology patients to review a hypothetical consent form for participation in a placebo-controlled, randomized clinical trial.²⁴⁸ One task given to the subjects was to interpret the meaning of four different statements in the consent form.²⁴⁹ Depending on the

245. See BRADFORD H. GRAY, *HUMAN SUBJECTS IN MEDICAL EXPERIMENTATION* 102-03 (1975); see also Angela Estey et al., *Are Research Subjects Able to Retain the Information They Are Given During the Consent Process?*, 3 *HEALTH L. REV.* 37 (1994). A study of twenty-nine subjects from two clinical trials at the University of Alberta Hospitals revealed that fourteen of them were unable to describe accurately the type of research study in which they were enrolled and seventeen could not list any risks associated with participation in the trial although risks had been explicitly explained to them. See *id.* at 40.

246. See CHARLES LIDZ ET AL., *INFORMED CONSENT: A STUDY OF DECISIONMAKING IN PSYCHIATRY* 28 (1984). In a 1987 article that appeared in the *Hastings Center Report*, further details were provided regarding informed consent in research studies involving psychiatric illness. See Appelbaum et al., *supra* note 238. The authors observed consent procedures in four research studies and interviewed subjects immediately after they gave their consent. They found that 69% of patients failed to comprehend the basis of their random assignment to treatment groups, and only 28% had a full understanding of the randomization procedure. Forty-four percent of participants in studies with a no-treatment or placebo control arm failed to realize that some enrollees who wished to receive treatment would not be given any. Thirty-two of eighty subjects with psychiatric illnesses stated that they believed the assignment would be made on the basis of their medical needs. In addition, "many of these subjects constructed elaborate but entirely fictional means by which an assignment would be made that was in their best interests." *Id.* at 21.

In one study that was observed, the investigator offered subjects detailed and voluminous information in a process that took several days, including one session in which the entire trial was reviewed. Nevertheless, half the patients did not grasp that treatment would be provided on a randomized basis, four of the twenty did not understand how placebos would be used, five did not comprehend the concept of double-blinding, and eight of the twenty believed that the drugs they would be given would be adjusted according to their own needs. *Id.* at 23.

The authors explain their findings as follows:

Most people have been socialized to believe that physicians (at least ethical ones) always provide personal care. It may therefore be very difficult, perhaps nearly impossible, to persuade subjects that *this* encounter is different, particularly if the researcher is also the treating physician, who has previously satisfied the subject's expectations of personal care. Further, insofar as much clinical research involves persons who are acutely ill and in some distress, the well-known tendency of patients to regress and entrust their well-being to an authority figure would undercut any effort to dispel the therapeutic misconception.

Id.
247. See DeRenzo et al., *supra* note 243, at 72; see also Holly A. Taylor, *Barriers to Informed Consent*, 15 *SEMINARS IN ONCOLOGY NURSING* 89, 91 (1999) (noting that oncology patients often perceive enrollment in a research protocol as their last chance to receive effective treatment).

248. See H. J. Sutherland et al., *Are We Getting Informed Consent for Patients with Cancer?*, 83 *J. ROYAL SOC'Y MED.* 439, 439-40 (1990).

249. See *id.* at 440.

statement, the subjects provided incorrect answers 26 to 54% of the time.²⁵⁰

Investigators who conducted three multinational studies in the 1980s, including clinicians from North America and Europe, were asked whether they believed that their human subjects had grasped the essential information that was given to them.²⁵¹ Forty-seven percent of responding doctors answered that they thought few patients knew they were participating in a controlled experiment, even though they had given written consent.²⁵² In two other studies, over three-quarters of responding physicians believed that their patients rarely understood all the information given to them.²⁵³

Some investigators, in fact, resent informed consent requirements. In one study, 34% of physicians said that they would enter more patients in clinical trials if they could dispense with informed consent altogether, and 95% expressed the belief that informed consent intruded into the doctor-patient relationship.²⁵⁴ Sixty-five percent believed "that the process of obtaining informed consent negatively altered patients' perceptions of the physicians' ability to individualize their care."²⁵⁵

During 1998 and 1999, OPRR suspended federal research funding at five well-regarded institutions, including Chicago's Rush-Presbyterian-St. Luke's Medical Center, the West Los Angeles VA Medical Center, Duke University Medical Center, the University of Illinois at Chicago, and six University of Colorado institutions.²⁵⁶ In 2000, research activities were suspended at the University of Pennsylvania, the University of Alabama at Birmingham, the University of Oklahoma's medical school in Tulsa, the University of Texas Medical Branch in Galveston, and the NIH campus in Bethesda, Maryland.²⁵⁷ Among the violations for which these entities were

250. *Id.* at 441.

251. *See* Edwards et al., *supra* note 223, at 1210.

252. *See id.* at 1209.

253. *See id.* at 1209-10.

254. Kathryn M. Taylor and Merrijoy Kelner, *Informed Consent: The Physicians' Perspective*, 24 SOC. SCI. & MED. 135, 137, 139 (1987). In this study breast cancer specialists from eight countries, including the United States, Canada, England, Scotland, Australia, France, Sweden, and Italy, were surveyed between January 1984 and February 1985. The physicians completed a questionnaire containing thirty-seven inquiries and were then interviewed individually for an hour. *Id.* at 135-36.

255. *Id.* at 140.

256. Vida Foubister, *More Centers Cited for Ethics Lapses in Research*, AM. MED. NEWS, Nov. 1, 1999, at 8, 10; *see also* AM. ASS'N FOR THE ADVANCEMENT OF SCI., PROFESSIONAL ETHICS REPORT 3 (Summer 1999) (noting that OPRR shut down one thousand human research studies at the University of Illinois at Chicago and investigated the University of South Florida's IRB).

257. Cmons, *supra* note 8, at 12-A (University of Pennsylvania); Reeves, *supra* note 8, at 12-A (University of Alabama); Kelly Kurt, *Officials Depart, Dismissed Amid Scandal at OU's Medical School*, JOURNAL RECORD, July 24, 2000; letter from Michael A. Carome, Chief, Compliance Oversight Branch, Division of Human Subject Protection, to Dorothy Wilson, Vice President for Research, University of Texas Medical Branch at Galveston, Sept. 14, 2000, at 6 (on file with author); Rich Weiss, *Child Research Study Halted*, WASH. POST, Nov. 7, 2000, at A25.

cited was the failure to obtain adequate informed consent from subjects.²⁵⁸

The Belmont Report establishes that the consent process contains three elements: information, comprehension, and voluntariness.²⁵⁹ Without the presence of all three, physicians cannot be said to be adequately fulfilling their duty of respect for persons, and subjects cannot be said to be adequately exercising their right of autonomy.²⁶⁰ In light of the plethora of evidence that many individuals today do not provide valid informed consent to participation in biomedical research, it appears that subject autonomy is often compromised in the contemporary research climate.

For this reason as well it is important to reduce to a minimum the potential dangers inherent in placebo-controlled clinical trials. If subjects were given the opportunity to choose to make great personal sacrifices for the sake of scientific inquiry, many people would likely opt for enrollment without fully comprehending the nature of the protocol and the extent of its hazards. They would therefore be jeopardizing their welfare without exercising meaningful autonomy.

3. *Gravely Ill Patients Constitute a Vulnerable Population That Requires Special Protection*

Obtaining valid informed consent is particularly difficult when the individuals at issue have life-threatening diseases. The subjects who would be most endangered by randomized clinical trials are those who would be foregoing life-saving therapy if they were assigned to a placebo arm. When these patients enroll in clinical trials, their decisions to do so often have significant implications for their medical futures. The autonomy of these patients, however, is often impaired by the emotional trauma of their illness or by various social and familial pressures.

The concept of justice, articulated in the Belmont Report, requires that vulnerable subjects receive special protection.²⁶¹ It further identifies seriously ill patients as a vulnerable population.²⁶² Specifically the Belmont Report states:

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their

258. See Foubister, *supra* note 256, at 8, 10; Cimon, *supra* note 8, at 12-A; see also U.S. DEP'T OF HEALTH & HUMAN SERVS., OFFICE FOR HUMAN RESEARCH PROTS., OHRP COMPLIANCE ACTIVITIES: COMMON FINDINGS AND GUIDANCE (Sept. 1, 2000), available at <http://ohrp.osophs.dhhs.gov/references/findings.pdf>.

259. Belmont Report, *supra* note 14, at 23,195.

260. See *id.*

261. See *id.* at 23,197. Protection of persons with diminished capacity is also integral to the concept of autonomy. See *id.* at 23,193.

262. *Id.* at 23,197.

ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.²⁶³

Illness has been described as an "ontological assault" that undermines the patient's identity by "attacking the fundamental unity of mind and body."²⁶⁴ A patient who suffers from multiple sclerosis described the experience of illness in these words:

The most deeply held assumption of daily life is the assumption that I, personally, will continue to be alive and it is in light of this assumption that one engages in daily activities. The onset of illness, however, brings one concretely face-to-face with personal vulnerability. . . . Thus, the person who is ill . . . is unable readily to fit illness into the typified schema used to organize and interpret experience. . . . One finds oneself preoccupied with the demands of the here and now, confined to the present moment, unable effectively to project into the future.²⁶⁵

Commentators have noted that serious sickness returns patients to an infantile state in which they wish to be cared for and to be free of the responsibility and stress of decisionmaking and acting.²⁶⁶ An example is the case of Dr. Franz Ingelfinger, the long-time editor of the *New England Journal of Medicine* and a world-renowned expert on diseases of the esophagus.²⁶⁷ When he was diagnosed with cancer of the esophagus, he found that his doctors expected him to determine how best to treat his own illness:

As a result, not only I but my wife, my son and daughter-in-law (both doctors), and other family members became increasingly confused and emotionally distraught. Finally, when the pangs of indecision had become nearly intolerable, one wise physician friend said, "What you need is a doctor." . . . When that excellent advice was followed, my family and I sensed immediate and immense relief.²⁶⁸

Many scholars have noted that the decisionmaking capacity of individuals suffering from prolonged or serious illnesses is often impaired and

263. *Id.*

264. MARK A. HALL, MAKING MEDICAL SPENDING DECISIONS 36 (1997).

265. *Id.* at 37.

266. *Id.*

267. *See id.*

268. *Id.*

have recommended that research protocols designed to involve such patients be subjected to heightened scrutiny by IRBs.²⁶⁹ Seriously ill patients may experience depression, extreme anxiety, rage, denial, or desperation to find a cure, all of which may cloud their judgment and their ability to evaluate the benefits and risks of a clinical trial.²⁷⁰ A study that focused on the informed consent process for patients with a range of disease severity found that as the seriousness of the illness increases, the ability of subjects to remember information relevant to their research participation decreases.²⁷¹ One prominent commentator has gone as far as to identify the terminally ill patient as "the most vulnerable research subject, the one most consistently transformed into an object (a mere means to an end)."²⁷²

It is overly optimistic and simplistic to expect that patients with terminal illnesses will have the capacity to evaluate a doctor's recommendation

269. See Alison Wichman, *Protecting Vulnerable Research Subjects: Practical Realities of Institutional Review Board Review and Approval*, 1 J. HEALTH CARE L. & POL'Y 88, 93 (1998) (stating that "people suffering from prolonged or serious illnesses that are refractory to standard therapies, or for which there are no standard therapies, should be considered vulnerable particularly when they are willing to take any risk for even a remote possibility of relief"); DeRenzo et al., *supra* note 243, at 69, 78 (stating that "the majority of studies conclude that seriously ill research subjects have difficulties in many facets of providing ethically valid consent," and "[s]erious disease produces desperation . . . [b]oth on the part of subjects and their families [that] can make persons vulnerable to manipulation"); George J. Annas, *The Changing Landscape of Human Experimentation Nuremberg, Helsinki, and Beyond*, 2 HEALTH MATRIX 119, 134 (1992) (stating that "[t]erminally ill AIDS and cancer patients can be harmed, misused, and exploited"); D. Christian Addicott, *Regulating Research on the Terminally Ill: A Proposal for Heightened Safeguards*, 15 J. CONTEMP. HEALTH L. & POL'Y 479, 493 (1999) (stating that "the terminally ill share a number of relevant characteristics with the vulnerable populations listed in the regulations, [and thus] an IRB would be well within its authority to treat the terminally ill as vulnerable"); Sarah Hewlett, *Consent to Clinical Research—Adequately Voluntary or Substantially Influenced?*, 22 J. MED. ETHICS 232, 233 (1996) (noting that patients dealing with illness may experience a reduction in their autonomy due to a variety of factors related to the physiologic and psychological impact of illness).

270. See Addicott, *supra* note 269, at 502-03; Hewlett, *supra* note 269, at 233.

271. See Monica H. Schaeffer et al., *The Impact of Disease Severity on the Informed Consent Process in Clinical Research*, 100 AM. J. MED. 261, 264 (1996). The study involved 127 subjects who were recruited from four different research protocols at the National Institutes of Health. Nine subjects had metastatic cancer for which all treatment had thus far failed and were offered a Phase I study. Thirty-six subjects had recurrent ovarian cancer and were offered a Phase II trial. Twenty-eight subjects were infected with the HIV virus and were offered participation in a Phase III clinical trial. Finally, fifty-four subjects were healthy volunteers who were enrolled in positron emission tomography studies. See *id.* at 261-62.

While the ability of patients to remember information associated with their clinical trial generally decreased as the severity of their illness increased, there were several exceptions to this finding. Immediate retention of information regarding clinical trial procedures increased as the severity of illness increased. In addition, Phase I and II subjects showed the best long-term retention, while Phase III participants and healthy volunteers retained the least on a long-term basis. Finally, retention of information about alternative therapies was the same among the three groups of sick subjects. See *id.* at 264; see also Barrie R. Cassileth et al., *Informed Consent—Why Are Its Goals Imperfectly Realized?*, 301 NEW ENG. J. MED. 896, 898 (1980) (noting that "[b]edridden patients gave significantly fewer correct responses to each item on the recall test [concerning chemotherapy, radiation therapy, or surgery, to which they had consented the previous day] than did ambulatory patients").

272. Annas, *supra* note 269, at 120.

concerning participation in a clinical trial fully and to reach an autonomous decision regarding the degree of personal sacrifice that they wish to make. Seriously ill patients constitute a vulnerable population that deserves special protection. One means of providing effective protection and counteracting diminished autonomy is to prohibit the implementation of placebo-controlled trials in which some patients must forgo standard treatment that would prolong or enhance their lives significantly.

C. *Physicians and IRBs as Protectors of Human Subjects*

Human subjects can expect to be protected by two groups of people involved in the research process—physicians and IRBs. Physicians are duty bound to promote the best interest of patients, and IRBs are responsible for research oversight. For a variety of reasons, however, both are limited in their ability to safeguard the welfare of human subjects. These limitations impair both the beneficence of medical professionals and subject autonomy. For this reason, too, further regulation of placebo-controlled trials is necessary.

1. *Investigators Serve in the Dual Role of Physicians and Researchers and Often Have Conflicts of Interest*

The complexity of the physician's role in the research setting also militates against the unrestricted utilization of placebos in clinical studies. Patients should not be given opportunities to participate in research that might significantly endanger their health because the judgment of those designing and conducting the research might be clouded by conflicts of interest.

When doctors serve as both treating physicians and researchers, they may possess competing interests. On the one hand, the physicians must act in the best interest of their patients. Simultaneously, however, the doctors must recruit patients to participate in their biomedical studies, testing therapies that are unproven and possibly unsafe. The conflict of interest is especially pronounced in blinded, randomized clinical trials, where the physician, in the interest of science, must deprive some patients of medication and withhold from individual subjects information regarding which treatment they will be receiving and what evidence exists regarding the efficacy of the experimental alternative.²⁷³

Complicating the role of physician-investigators are the conflicting personal motivations they might experience when engaging in biomedical research. While wishing to fulfill their responsibilities towards their patients, they may also be lured by the appeals of accomplishment, fame,

273. See David S. Shimm & Roy G. Spece, Jr., *An Introduction to Conflicts of Interest in Clinical Research*, in *CONFLICTS OF INTEREST IN CLINICAL PRACTICE AND RESEARCH* 362 (Roy G. Spece, Jr. et al. eds., 1996).

recognition, publication, and pecuniary gain from the research.²⁷⁴ Drug companies often provide very generous payments to private physicians who conduct clinical drug studies and successfully recruit large numbers of human subjects.²⁷⁵ For the most aggressive recruiters, these payments can total between \$500,000 and \$1,000,000 annually, an amount that is extremely alluring for physicians, who are otherwise often restricted in their earning capacities by managed care.²⁷⁶ These factors may induce physicians to pressure patients to participate in clinical studies even when enrollment is clearly not in their best interest. If placebo utilization is permitted only in instances in which patients who forego treatment will not be exposed to the threat of death, disability, extreme or lasting pain or long-term injury, the adverse consequences of potential conflicts of interest will be minimized.

In addition, physician-investigators come under pressure to fulfill high expectations that are held not only by patients, but also by colleagues, the sponsors of the clinical trial, and the institutions at which the trials are conducted.²⁷⁷ These different obligations may also lead to serious conflicts of interest.

Since academic institutions rely on grant funding for their revenues, research proposals must be produced and completed rapidly to assure grant support.²⁷⁸ Investigators are consequently under considerable pressure to recruit subjects as quickly as possible in order to generate money to support their institutions' buildings, laboratories, staff, and salaries.²⁷⁹

Furthermore, private industry has become an increasingly important source of research funding.²⁸⁰ In 1989 private industry contributed \$9.26 billion for health research and development.²⁸¹ By 1995 industry expenditures for health-related research totaled \$18.6 billion, and in 2000 pharmaceutical companies invested \$22.4 billion in research.²⁸²

One recent study found that clinical trials funded by pharmaceutical companies were nearly eight times less likely to reach unfavorable qualitative conclusions than were those funded by nonprofit sources and 1.4 times more likely to reach favorable qualitative conclusions.²⁸³ In addition, one

274. *See id.*

275. *See* Eichenwald & Kolata, *supra* note 4, at 34.

276. *See id.*

277. *See* Shimm & Spece, *supra* note 273, at 362.

278. *See* Katz, *supra* note 183, at 38.

279. *Id.*

280. *See* Shimm & Spece, *supra* note 273, at 370.

281. *Id.*

282. NATIONAL BIOETHICS ADVISORY COMMISSION, ETHICAL AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS ch. 1, at 4 (draft report Dec. 19, 2000).

283. *See* Mark Friedberg et al., *Evaluation of Conflict of Interest in Economic Analyses of New Drugs Used in Oncology*, 282 JAMA 1453, 1455 (1999). Many of the studies reached neutral conclusions, including 35% of those funded by pharmaceutical companies and 21% of those funded by nonprofits.

out of five articles describing study results were found to contain "qualitative overstatements of quantitative results."²⁸⁴ The study provides the following analysis:

[P]harmaceutical companies can influence research in a variety of ways. Studies may be funded through unrestricted research grants, educational funds, or consultancies (paid directly to investigators). These may include contractual agreements requiring pharmaceutical company review of manuscripts before being submitted for publication. Researchers also may receive funding from the same companies in the form of honoraria or travel awards for scientific meetings and have equity interests in companies and profit directly from increased drug sales. It is possible that these factors may result in some unconscious bias (perhaps when qualitatively interpreting results) that could influence study conclusions.²⁸⁵

Some commentators have contended that doctors are willing to enter patients in placebo-controlled clinical trials even when potentially life-saving therapy is at issue. A study published in the *British Medical Journal* found that 53% of doctors who preferred tamoxifen treatment for early breast cancer were prepared to enter their patients in a placebo-controlled trial even though the patients' survival might be at stake.²⁸⁶ Seventy-three percent of responding physicians indicated that a trial of hormone replacement therapy in patients treated for breast cancer would be ethical, even though only 28% were "'uncertain' whether this treatment could provoke a recurrence of this hormone sensitive tumour," and the others apparently believed that it could cause a recurrence.²⁸⁷

It is also important to note that DHHS regulations do not require disclosure of conflicts of interest to patients.²⁸⁸ Patients thus often remain unaware of the fact that, in recommending enrollment in a clinical trial, the physician might be induced by the incentives of personal or institutional gain. In making their decisions regarding participation in biomedical research, patients are unable to evaluate the investigators' own motivations and therefore cannot always engage in fully educated assessments.²⁸⁹ Their

284. *Id.*

285. *Id.* at 1456.

286. Edwards et al., *supra* note 223, at 1211.

287. *Id.* The authors note that it is possible that some patients might have wanted to trade off some survival advantage in return for a relief of symptoms.

288. See 21 C.F.R. §§ 50.25(a)-(b) (1999); 45 C.F.R. §§ 46.116(a)-(b) (1998). The regulations list numerous items that must be disclosed to potential human subjects. Conflicts of interest, however, are not mentioned and thus are not among the issues that have to be discussed with participants.

289. I am not arguing that researchers should necessarily discuss conflicts of interest with patients. Patients who are told that their physician may have a conflict of interest when recommending participation in a clinical trial will not be able to utilize the information in a meaningful way and will simply be confused and lose trust in their doctor. Unlike scientific data such as potential risks and benefits, the inner-workings of the investigator's psyche and ego cannot be assessed by a patient for purposes of

autonomy is consequently compromised.

Conflicts of interest also jeopardize the value of beneficence. An investigator whose judgment is clouded by the allure of personal or institutional gain may not do everything possible to maximize potential benefits and minimize harms to human subjects.

Physician and philosopher Edmund Pellegrino identified three conflicting values in clinical research: "for science, it is truth; for medicine, it is beneficence toward the patient; and for the investigator as an individual, it is self-interest."²⁹⁰ He concluded that

[t]he safe rule in [clinical research] is to favor beneficence over scientific rigor when the two seem to be in conflict or when in doubt. The possible loss of knowledge cannot outweigh the possibility of harm to the subject even if the utilitarian calculus indicates great benefit to many and harm to only a few.²⁹¹

Because of likely conflicts of interest, placebo-controlled trials that pose significant dangers to patients should be prohibited. Conflicts of interest threaten both beneficence and patient autonomy. Doctors, whose decisions might be tainted by selfish or economic motivations, should not be able to choose to place patients at risk of serious harm in clinical studies. Limiting the circumstances in which placebo usage is permitted, as suggested in the guidelines outlined in Part VI below, will minimize concerns stemming from conflicts of interest.

2. IRBs, As They Are Currently Constituted, Provide Insufficient Oversight for Clinical Trials

Further attention must be focused on IRBs as the primary oversight institution for biomedical research. Federal regulations provide that it is the duty of the IRB reviewing the research protocol to ensure that informed consent is sought from each subject.²⁹² In addition, according to the regulations, IRBs must not allow research to proceed if risks to the subjects are not minimized and are not reasonable in relation to anticipated benefits, regardless of whether some individuals might be willing to jeopardize their health by participating in unsound trials.²⁹³

A recent statement issued by DHHS's Office of Inspector General is

informed consent. After disclosure, the patient will not know whether the physician is truly swayed by selfish motives or whether the researcher is a person of integrity who is disclosing the potential conflict only out of an abundance of caution. Therefore, the existence of conflicts of interests is discussed here only as an additional reason for limiting the circumstances in which placebo controls should be utilized and not as a basis for additional informed consent requirements.

290. Edmund D. Pellegrino, *Beneficence, Scientific Autonomy, and Self-Interest: Ethical Dilemmas in Clinical Research*, GEOGRAPHICA MEDICA 21 (1991).

291. *Id.* at 27.

292. See 21 C.F.R. § 56.111(a)(4) (1999); 45 C.F.R. § 46.111(a)(4) (1998).

293. See 21 C.F.R. §§ 56.111(a)(1)-(2) (1999); 45 C.F.R. §§ 46.111(a)(1)-(2) (1998).

highly critical of the IRB system.²⁹⁴ The report criticized IRBs for failing to conduct conscientious continuing reviews of research studies that have previously been approved.²⁹⁵ IRBs review only written reports that are submitted by investigators conducting the clinical trials.²⁹⁶ They generally do not visit research sites, oversee the consent process, or seek feedback from subjects.²⁹⁷ The continuing review mechanism is thus one of self-reporting by investigators and does not provide thorough oversight. The current system, presumably, leaves ample opportunity for irresponsible researchers to abuse the system and their human subjects.

The Office of Inspector General further found that IRB members and investigators are insufficiently trained to address the complex ethical and scientific questions with which they are faced.²⁹⁸ The report asserted that IRBs have a dearth of resources available for educational programs and that members and researchers are often reluctant to attend training sessions when they are offered.²⁹⁹

As IRBs are now constituted, the vast majority of their members are busy professionals who volunteer their time to the IRB and do not receive any compensation. According to the OPRR, 86% of IRB members in 1995 were affiliated with academic research institutions as full-time faculty (56%), clinical and research staff (18%), and administrators (6%).³⁰⁰ The 491 IRBs included in OPRR's study had memberships that ranged from five to forty-four.³⁰¹ The number of protocols submitted for IRB review has increased by approximately 42% during the past five years, and some IRBs now evaluate as many as 2,000 proposed studies each year.³⁰² A 1996 U.S. Government Accounting Office report found that in some cases IRBs spend only one or two minutes reviewing each study because of the number of proposals on their agendas, at times as many as 150 to 200 per meeting.³⁰³

With this volume of work, it is unrealistic to expect IRB members also to visit research sites and interview subjects for purposes of continuing

294. See *Hearing*, *supra* note 241 (statement of George Grob).

295. See *id.*

296. See *id.*

297. See *id.*

298. See *id.*

299. See *id.*

300. JAMES BELL ET AL., EVALUATION OF NIH IMPLEMENTATION OF SECTION 491 OF THE PUBLIC HEALTH SERVICE ACT, MANDATING A PROGRAM OF PROTECTION FOR RESEARCH SUBJECTS, FINAL REPORT 17 (1998), available at http://ohrp.osophs.dhhs.gov/hsp_report/hsp_final_rpt.pdf. The Office for Protection from Research has been renamed the Office for Human Research Protections, U.S. Department of Health and Human Services.

301. *Id.*

302. See *Hearing*, *supra* note 231 (statement of George Grob).

303. U.S. GENERAL ACCOUNTING OFFICE, NO. GAO/HEHS-96-72, REPORT TO THE RANKING MINORITY MEMBER, COMMITTEE ON GOVERNMENTAL AFFAIRS, U.S. SENATE, SCIENTIFIC RESEARCH: CONTINUED VIGILANCE CRITICAL TO PROTECTING HUMAN SUBJECTS 14 (1996).

review. There is no doubt, however, that effective continuing review is essential to the integrity of biomedical research. Meaningful oversight is particularly important for protocols involving placebo controls, where a portion of the subjects will be deprived of both the experimental treatment and standard therapy. Irresponsible or unethical practices on the part of investigators that are not detected and prohibited by IRBs may seriously jeopardize the health of the subjects in the placebo arm.

One cannot assume that the welfare of the subjects is always the investigator's first priority and that IRBs are always able to conduct the thorough review of each protocol that is intended by existing federal regulations. Consequently, investigators and IRBs cannot be given unlimited discretion as to when to permit the utilization of placebos in clinical studies. Investigators, IRBs, and human subjects would all profit from the implementation of further guidance regarding this issue.

VI. RECOMMENDATIONS

The efficiency of placebo controls and the subjects' right of autonomy justify the retention of placebo controls as a component of biomedical research. However, investigators should not be permitted to utilize placebo controls indiscriminately, because in some circumstances they expose patients to unacceptable risks. Furthermore, it is unlikely that the problems of imperfect informed consent, the vulnerability of gravely ill patients, conflicts of interest, and insufficient institutional oversight will be completely eliminated in the near future. Permitting the use of placebo controls only when the risks to human subjects are small is essential to the safety of clinical research. Currently, DHHS and the FDA provide no specific guidelines as to the circumstances in which the use of placebo controls is appropriate. A suggested approach is described in this section.

A. *Placebo Controls Should Be Used Only in Limited Circumstances*

The inclusion of placebo-control arms in clinical trials for first-line therapies is appropriate.³⁰⁴ Therapies for a condition that has been previously untreatable can be compared only to a placebo or no treatment control since there is no other intervention against which their efficacy can be measured.³⁰⁵ Similarly, clinical trials assessing treatments for patients who are resistant to or cannot tolerate conventional therapy should utilize placebo controls, since active controls would be of no benefit and perhaps of significant harm to participants.³⁰⁶

Utilization of placebo controls in circumstances other than those listed

304. See Freedman et al., *supra* note 11, at 250.

305. See *id.*

306. See *id.*

above, however, is ethically more problematic. Placebos should not be utilized in studies relating to serious, irreversible, or life-threatening conditions for which effective therapy exists if there is any chance that the patient will suffer lasting harm or severe, prolonged discomfort as a result of being deprived of treatment.³⁰⁷ If, however, a patient would not be exposed to the threat of death, disability, severe or lasting pain, or long-term injury by assignment to the placebo arm of a clinical trial, the use of placebos should be permitted so long as sufficient safeguards are implemented to protect the welfare of all subjects. Protocols involving sham surgeries should be subjected to the highest level of scrutiny since they expose patients to the risks of anesthesia and deep incisions.³⁰⁸

In addition, placebo-controlled clinical trials in which patients will not risk death, disability, severe or lasting pain, or long-term injury should be designed to meet the following three requirements. First, patients receiving placebos should be carefully and frequently monitored. Second, early escape mechanisms, providing for discontinuation of the subject's participation in the study, must exist for patients who suffer adverse consequences from the lack of active therapy.³⁰⁹ Third, the clinical trial's duration should be kept as short as possible.³¹⁰

It would be ethical, for example, to include a placebo arm in a short-term clinical trial for a new drug for mild to moderate hypertension with

307. See Nightingale, *supra* note 13, at 498; CEJA OPINION, *supra* note 42. The AMA states that "[p]rotocols that involve conditions causing death or irreversible damage cannot ethically employ a placebo control if alternative treatment would prevent or slow the illness progression." CEJA OPINION, *supra* note 42. With respect to conditions characterized by "severe or painful symptoms," the AMA advises researchers to thoroughly explore the use of controls other than placebos and states that "the more severe the consequences and symptoms of the illness under study, the more difficult it will be to justify the use of a placebo control when alternative therapy exists." *Id.* This Article recommends that investigators be given somewhat less flexibility and that placebos never be employed if the patient is likely to suffer severe or prolonged discomfort that could be avoided by the use of standard therapy.

308. Since sham surgeries are a recent research phenomenon there is only very limited evidence regarding their consequences for patients. Dr. Baruch Brody, a prominent ethicist, approved a clinical trial involving sham surgeries for arthritic knee pain despite significant initial hesitation. He became convinced that the trials were sufficiently safe for human subjects and were scientifically worthwhile. Talbot, *supra* note 31, at 35. At this time I do not support a ban on placebo controls in the form of sham surgeries. However, if further evidence reveals that patients suffer severe adverse consequences as a result of these procedures, it would be appropriate to prohibit the practice.

309. See Joyce A. Cramer, *Ethical Issues in The Planning and Conduct of Clinical Trials of Anti-Epileptic Drugs*, 16 MED. & L. 209, 210 (1997) (discussing the use of placebos in short-term, in-patient protocols with intensive monitoring, and stating that "[t]he essential feature of such protocols is an 'escape clause' that stops the protocol when a patient experiences more seizures"). See also FDA INFORMATION SHEET, *supra* note 13, at 7.

310. See FDA INFORMATION SHEET, *supra* note 13, at 7; CEJA OPINION, *supra* note 42. No specific guidelines can be provided as to the desirable length of placebo-controlled trials, since each must be assessed on an individual basis depending on the conditions and medications being studied. Patients suffering from mild to moderate hypertension, for example, could possibly receive a placebo for several weeks if they are carefully monitored. Patients in a study for pain medication, on the other hand, may be able to endure the discomfort for only a few hours.

the implementation of extensive monitoring and an escape clause. Participants who suffer from hypertension would be monitored as frequently as investigators deem appropriate to ensure that their blood pressures do not rise to dangerously high levels.³¹¹ If a patient develops a life-threatening change in blood pressure, the individual would be withdrawn from the trial and would begin receiving standard therapy immediately.³¹² Patients in such a trial would have to understand that they will be required to visit the doctor for monitoring more frequently than is ordinarily necessary.

Similarly, it would be ethical to include a placebo in a clinical trial for medication designed to treat moderate pain or nausea so long as patients are carefully monitored and allowed to discontinue participation if they no longer wish to endure the discomfort. Placebo usage would obviously be inappropriate in a study involving post-operative pain that is generally severe and may be insufferable without potent medication. For less severe pain, however, patients could be given either medication or placebos at the clinic and asked to spend several hours there for observation. After a certain time period such as two hours, patients receiving placebos who have not experienced relief and who no longer wish to suffer the discomfort could be given standard treatment to relieve their symptoms.

Placebo-controlled clinical trials should be designed to be of a sufficient length to obtain accurate statistical results. However, since some patients in such trials receive no treatment, the trials should not be continued longer than absolutely necessary for research purposes. Investigators planning placebo-controlled clinical trials must make every effort to determine the optimal length of time for the study and ensure that the study's duration is as short as possible.³¹³

Limiting the utilization of placebo controls to the circumstances outlined above will ensure that risks to subjects are minimized, as mandated

311. Both participants receiving the placebo and those receiving the experimental drug should be monitored with the same frequency since both have a risk of suffering consequences that would not occur with standard therapy. If standard treatment is provided in a third arm of the clinical trial, patients receiving the conventional therapy should also be monitored with the same frequency in order to maintain blinding and avoid identifying the patients in the different trial groups.

312. However, patients should not have their medication changed abruptly if such a change will further threaten their health. See LEVINE, *supra* note 123, at 44.

313. Another option available to investigators is crossover placebo-controlled trials. In these studies, patients who received a placebo are switched to the experimental therapy halfway through the trial, and those who took the experimental treatment are given a placebo for the remainder of the study's duration. *Id.* at 207. This design ensures that all patients have an opportunity to benefit from the experimental drug during half of their enrollment period. However, crossover placebo-controlled trials have been criticized for exacerbating the problem of placebo usage. In these trials all of the participants (instead of just half) are deprived of active therapy at some point. *Id.* Also, crossover trials could be more expensive than regular placebo-controlled studies if they are designed to be long enough so that each group receives a full course of the treatment. Rather than have just one group receive a course of the medication and the other receive a placebo during the same time, a crossover trial may provide each group with a full course of the treatment at different times.

by existing federal regulations.³¹⁴ The recommendations seek to protect research participants so that the risks to which they are exposed are "reasonable in relation to anticipated benefits, if any, to [them] and the importance of the knowledge that may be expected to result."³¹⁵

Guidelines concerning the utilization of placebo controls, however, must be flexible enough to be applied to a wide spectrum of research studies and research needs. Consequently, they cannot draw bright lines or provide a specific formula that can mechanically be followed. The recommended guidelines are designed to provide a realistic and practical framework for the assessment of placebo-controlled clinical trials.

B. *Placebo-Controlled Studies in Developing Countries*

Randomized placebo-controlled clinical trials in developing countries involve unique problems and ethical dilemmas.³¹⁶ A full discussion of these issues is beyond the scope of this Article. A few points, however, should be made. The Declaration of Helsinki was revised in 2000 partly in response to the use of placebos in research studies in developing countries.³¹⁷ It now prohibits any use of placebos unless no standard therapy exists for the condition in question.³¹⁸ This Article rejects the Declaration of Helsinki's absolutist position not only with respect to research conducted in the United States, but also with respect to international clinical trials.

It is clear that clinical studies that utilize Third World populations to test drugs for use solely in developed countries are unethical.³¹⁹ If the intervention being tested will not be available in the country providing the research subjects, then the sponsor nation is simply exploiting participants in order to gain knowledge inexpensively for its own benefit.³²⁰ In addition, if the research study can utilize an active control that is available in the developing country and failure to do so will cause irreversible harm, disability, significant pain, or death to the human subjects, employment of a placebo control should be prohibited.

314. 21 C.F.R. § 56.111(a)(1) (1999); 45 C.F.R. § 46.111(a)(1) (1998).

315. 21 C.F.R. § 56.111(a)(2) (1999); 45 C.F.R. § 46.111(a)(2) (1998).

316. See *supra* Part II.D.2. Ethicists are particularly concerned about whether clinical trials in developing countries are consistent with the requirements of justice. Cf. Belmont Report, *supra* note 14, at 23,193-94. Inclusion of impoverished populations in developing nations can constitute an unfair distribution of the burdens of scientific research. In many cases these subjects are less likely to enjoy the benefits of the research than would subjects in a developed nation, and researchers who are working in distant countries might be tempted to be less than meticulous about safeguarding the welfare of trial participants. Joe Stephens, *Where Profits and Lives Hand 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.

317. See Okie, *supra* note 188.

318. DECLARATION OF HELSINKI, *supra* note 21.

319. Annas & Grodin, *supra* note 114, at 561.

320. *Id.*

The use of placebos instead of standard therapy that could prolong or significantly enhance the subjects' lives may be justifiable only when a clinical trial is designed to study a new therapy for a serious condition that, while treatable in developed nations, is at the time untreatable in a Third World country. If subjects in the placebo arm of the study are not deprived of any treatment that they could otherwise receive in their country, utilization of placebos is not necessarily objectionable.

However, before being permitted to implement a placebo control in a developing country, researchers should be required to show that utilization of an active control consisting of standard therapy in the sponsor nation is not feasible. The impracticability may arise because of cost, the structure of the healthcare system in the country in question, or some factor related to the active control itself. For example, if a trial with an active control would be so expensive that researchers would choose not to conduct the study and consequently no affordable alternative would become available to the impoverished population, placebo usage would be acceptable. Similarly, if the developed nation's standard therapy requires hospitalization in a modern, well-equipped facility, and the trial is designed to explore an alternative for impoverished rural populations in Third World countries, an active control may be impossible to utilize because of the absence of modern hospitals in the relevant locale. Researchers should not be subjected to unrealistic standards and thus discouraged from developing effective and affordable therapies for Third World populations. However, absent such justifications, investigators must not be authorized to implement placebo controls.

C. The Suggested Guidelines Should Be Incorporated Into FDA and DHHS Regulations

The specific guidelines suggested above should be incorporated into the Code of Federal Regulations. The FDA regulation describing the five options for design of clinical trials³²¹ should include detailed instructions regarding the circumstances in which placebo controls are appropriate.

The FDA, however, regulates only drugs and devices, and its regulations are inapplicable to other types of treatments such as surgeries or bone marrow transplants.³²²

In light of recent studies involving sham surgeries, the guidelines should also be incorporated into DHHS regulations that apply to clinical trials outside the scope of FDA jurisdiction.³²³ DHHS regulations currently do not include any discussion of placebo utilization in clinical trials. Therefore, the guidelines cannot be incorporated into an existing provision,

321. See 21 C.F.R. § 314.126(b)(2) (1999).

322. See 21 C.F.R. § 7.3(f) (1997); see also Daniels & Sabin, *supra* note 132, at 29; Saver, *supra* note 132, at 1109-11.

323. See 45 C.F.R. § 46.101 (1998).

but rather, a new section will have to be added to address this issue.³²⁴

One might argue that IRBs are currently incapable of assuring that human subjects are sufficiently protected in placebo-controlled trials. While further resources must be invested in enhancing IRB oversight, specific guidelines regarding the appropriate utilization of placebo controls will facilitate the task of IRBs and allow them to judge the safety of the trials even in a very limited amount of time. If use of placebos is formally restricted to circumstances in which they will not significantly endanger human subjects and if investigators are required to describe the safeguards they have implemented in the protocols submitted to the IRB and the informed consent document provided to patients, the task of the IRB reviewing the proposed trial will be considerably easier. IRBs will be able to determine quickly whether the protocol meets regulatory requirements and provides adequate protection for human subjects.

VII. CONCLUSION

Randomized placebo-controlled clinical trials must be carefully designed by investigators and thoroughly scrutinized by IRBs to ensure that participants in the placebo arm will not be subjected to the risk of death, permanent disability, long-term harm, or pain that is prolonged or severe. If such risks do exist, investigators should utilize active or historical controls rather than placebos. Further regulations should be developed by DHHS and the FDA to elucidate the circumstances in which the use of placebos is appropriate and to ensure the integrity of the informed consent and continuing review processes. However, placebo controls need not be eliminated from clinical research. Short-term placebo-controlled trials that are subjected to a conscientious review by IRBs and feature frequent, careful monitoring and early escape clauses are appropriate for some treatments.

The use of placebo controls under suitable circumstances is justified by their efficiency and by the patient's right of autonomy. At the same time, the doctrines of autonomy and beneficence would prohibit the use of placebo controls in cases that could place the subject's health or welfare in jeopardy. In light of the researchers' potential conflicts of interest, the doubts that have been cast upon the ability of human subjects to provide informed consent, and the vulnerability of gravely ill patients, the use of placebo controls must be carefully regulated and restricted. It is only with appropriate safeguards that placebo-controlled clinical trials can remain a

324. Clinical trials involving sham surgeries that are not conducted, supported, or regulated by any federal department or agency are not subject to federal regulation. See 45 C.F.R. § 46.101(a) (1998). The guidelines suggested in this Article, therefore, could not be enforced with respect to such studies. This Article does not address the issue of whether research that is currently outside the scope of federal regulation should be subjected to regulatory oversight in the future.

useful component of biomedical research that serves the needs of patients, medical science, and society at large.