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Conflict + (and) Interest: Financial Incentives and Informed Consent in Human Subject Research

Shannon Benbow

NOTES

CONFLICT + INTEREST: FINANCIAL INCENTIVES AND INFORMED CONSENT IN HUMAN SUBJECT RESEARCH

SHANNON BENBOW*

I. INTRODUCTION

> *"The issue of patient protection is, at its very root, an ethical question—not simply a legal or scientific question."*[1]

During the 1980s, stock in biotechnology companies became increasingly profitable. These companies worked with institutional hospitals and research centers to develop drugs and potentially life-saving treatments. The companies relied on physicians at the hospitals and research centers to oversee and develop medical research. In turn, those companies often gave the physicians financial incentives in the form of stock options and licensing agreements. Until recently, that practice remained virtually unquestioned. Health care for profit became the standard, both in routine medical care, such as Health Maintenance Organizations, and in clinical research. That changed in 1999 when allegations of financial conflicts of interest and lack of informed consent surfaced in a lawsuit involving gene therapy at the University of Pennsylvania.

In 1998, Jesse Gelsinger died while participating in a gene therapy study at the University of Pennsylvania's Institute for

* J.D. Candidate, Notre Dame Law School, 2003; White Scholar, Thomas J. White Center on Law & Government, 2001–2003; B.A., Seattle Pacific University, 2000. Thank you to Kate Meacham for her helpful editorial comments, and to my parents, Barry & Debbie Benbow, for their support and encouragement.

1. REPORT OF THE COMMITTEE ON PATIENT PROTECTION IN RESEARCH TRIALS § I(B) (Sept. 6, 2001), *at* http://www.fhcrc.org/response/patientprotection committee_report.html (on file with the Notre Dame Journal of Law, Ethics & Public Policy) [hereinafter HUTCH PATIENT PROTECTION REPORT].

Human Gene Therapy ("IHGT").[2] Gelsinger suffered from a mild form of a rare metabolic disorder.[3] Although the therapy offered no benefit to him, Gelsinger agreed to participate in the study to benefit others born with a more serious form of the condition.[4] Gelsinger's family and his estate brought suit against those administering the experiment alleging, among other things, that Gelsinger's physicians failed to obtain his informed consent.[5] According to the complaint, Dr. James Wilson, then director of IHGT, founded Genovo, a biotech firm that provided funding and stock options to IHGT.[6] Because of their financial stakes in Genovo, the complaint stated, the defendants stood to gain financially from the success of the gene therapy experiment.[7] This fact, the plaintiffs alleged, proximately caused the death of Jesse Gelsinger on September 17, 1999.[8] The plaintiffs asserted that the defendants failed to obtain Gelsinger's informed consent because they did not adequately disclose the extent of Dr. Wilson's and the University's financial interests in the studies.[9]

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2. Complaint of John Gelsinger ¶ 1, Gelsinger v. Trustees of the Univ. of Penn., *available at* http://www.sskrplaw.com/links/healthcare2.html (last visited Oct. 13, 2002) (on file with the Notre Dame Journal of Law, Ethics & Public Policy).

3. *Id.* ¶ 2.

4. *Id.*

5. *Id.* ¶¶ 110(e)–(f).

6. *Id.* ¶¶ 13–18. The relevant allegations state:

13. At all times relevant hereto, Dr. Wilson was the founder of defendant Genovo, a biotech company. At all times relevant hereto, Dr. Wilson controlled up to thirty percent (30%) of the Genovo company stock.

14. Genovo agreed to provide the IHGT with over four million dollars a year for five years to conduct genetic research and experimentation.

15. In lieu of up-front payments to the University, Genovo transferred five percent (5%) equity ownership to the University.

16. In return for Genovo's sponsorship of genetic research and experimentation, the University agreed to grant Genovo licenses for the lung and liver applications for existing technologies developed by defendant, Dr. Wilson.

17. Defendant, Genovo, retained an option to negotiate for licenses for any future developments by defendants, IHGT and/or Dr. Wilson.

18. The proposed licenses between the defendants included full patent reimbursement, milestone payments and royalties on product sales.

7. *Id.* ¶¶ 35–36.

8. *Id.* ¶ 111.

9. *Id.* ¶¶ 110(e)–(f).

The Gelsinger case opened discussions of the extent of informed consent in research trials. The plaintiffs settled the case,[10] and other courts have not yet ruled on the specific issue. While the medical, legal, and patient communities continue to debate the issue, many physicians and institutions still receive funding and financial incentives from biotech companies, often without disclosing those incentives in obtaining informed consent.[11] Two recent cases, filed against the Fred Hutchinson Cancer Research Center ("Hutch") in Seattle, not only highlight the issue, but also illustrate its prevalence in the medical community.

The Hutch, described as the "Mecca" of cancer care centers, enjoys a solid reputation in both the scientific and patient communities.[12] Its staff includes two Nobel Prize Laureates,[13] and its federal grants in 2000 totaled $142 million.[14] In 2001, plaintiffs in two separate cases filed suits against the Hutch in Seattle, certain physicians there, and Genetic Systems Corporation, a biotech firm.[15] In one case, the plaintiff alleged that Kathryn Hamilton, a Hutch patient, died as a result of participation in a

10. Gelsinger Settlement Press Release, *at* http://www.sskrplaw.com/gene/pressrelease.html (last visited Apr. 30, 2002) (on file with the Notre Dame Journal of Law, Ethics & Public Policy).

11. To illustrate the pervasiveness of the issue, in June 2002, the New England Journal of Medicine loosened its policy regarding publication of evaluations of drugs by physicians who have a financial interest in the drug. Under the new policy, the Journal will refuse publication to physicians only if they have "significant" financial interests in manufacturers of the product, or their competitors. Under the old policy, the Journal refused publication to physicians with *any* financial interests in the manufacturer or its competitors. Jeffrey M. Drazen, M.D. & Gregory D. Kurfman, M.D., *Financial Associations of Authors*, 346 NEW ENG. J. MED. 1901 (2002).

12. *The Hutch is a Major Player in Cancer Care and Research*, SEATTLE TIMES, Mar. 11, 2001, at A17.

13. FRED HUTCHINSON CANCER RES. CENTER, *Our Nobel Prize Laureates*, *at* http://www.fhcrc.org/visitor/nobel/ (last modified June 18, 2002) (on file with the Notre Dame Journal of Law, Ethics & Public Policy).

14. *The Hutch is a Major Player in Cancer Care and Research*, *supra* note 12.

15. Berman v. Fred Hutchinson Cancer Research Ctr., No. C01-0727R (W.D. Wash. filed May 18, 2001), *available at* http://www.sskrplaw.com/gene/berman/complaint.html (complaint) (last visited Apr. 30, 2002) (on file with the Notre Dame Journal of Law, Ethics & Public Policy), *available at* http://www.fhcrc.org/response/126_681/legal/berman_response.pdf (response) (last visited Apr. 30, 2002) (on file with the Notre Dame Journal of Law, Ethics & Public Policy); Wright v. Fred Hutchinson Cancer Research Ctr., No. C01-5217RSL (W.D. Wash. filed Mar. 29, 2001), *available at* http://www.sskrplaw.com/gene/wright/complaint1.html (complaint) (last visited Apr. 30, 2002) (on file with the Notre Dame Journal of Law, Ethics & Public Policy), *available at* http://www.fhcrc.org/response/126_681/legal/litigation_response.pdf (response) (last visited Apr. 30, 2002) (on file with the Notre Dame Journal of Law, Ethics & Public Policy). Because these cases are still pending as of the date of this

study designed to develop a drug combination that would counter some of the effects of high doses of chemotherapy, a drug routinely administered to cancer patients.[16] In the other case, a class of plaintiffs alleged that the Hutch and defendant physicians, as a result of an agreement with Genetic Systems, earned substantial profits after concealing some risks and misrepresenting the study in which the patients participated, Protocol 126.[17] Both complaints allege that the researchers actively concealed certain material information from the patients because they stood to gain financially from the success of the experiments.[18] The cases against the Hutch highlight the extent of the issue, drawing particular attention to the fact that even reputable institutions are not shielded from allegations of patient mistreatment.

With the recent attention to the issue of patient protection in clinical research in general, and disclosure of financial incentives in obtaining informed consent in particular, Representative Diana DeGette introduced a bill in May 2002 aimed at reforming patient protections.[19] This Note will examine the issue of patient protection and financial incentives in medical research in the context of the doctrine of informed consent, detailing informed consent, from the reasons behind its inception to early cases promulgating the basic elements of the doctrine. Next, this Note will discuss the current state of the doctrine, including instances in which courts have extended the doctrine to issues beyond medical risks, examining the role of Institutional Review Boards in approving research and reviewing patient consent forms. Finally, this Note sets forth recommendations for potential changes, both in the law and within the medical research community.

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note, they are not discussed at length. Reference to them is meant to illustrate the on-going conflict regarding this issue.

In March 2001, the Seattle Times published an investigative report detailing the complaints in these two cases. *See infra* note 191.

16. Complaint of Allan Berman, *supra* note 15. Physicians generally administer high doses of chemotherapy in preparation for a bone marrow transplant.

17. Complaint of William Lee Wright, *supra* note 15, ¶ 21.

18. Complaint of Allan Berman, *supra* note 15, ¶ 101; Complaint of William Lee Wright, *supra* note 15, ¶ 21(10).

19. *See infra* notes 190–212 and accompanying text.

II. THE INFORMED CONSENT DOCTRINE

A. *The Roots of Informed Consent*

The Hippocratic Oath ("Oath") established the physician's duty to the patient.[20] The first sentence of the Oath is simple, yet straightforward: "Above all, do no harm."[21] The Oath further states, "I will use my power to help the sick to the best of my ability and judgment; I will abstain from harming or wrongdoing any man by it."[22] Today, the Oath provides a foundation for medical ethics. It sets forth the physician's duty to work in the best interest of the patient, and to avoid harming, or suggesting treatments that will harm, the patient.[23] Physicians still endeavor to abide by its mandates, making medicine a highly regarded profession.

1. The Nuremberg Code

Despite the mandates of the Hippocratic Oath, however, history shows that some physicians used their knowledge and position to harm patients, often under the umbrella of medical research.[24] The most notorious of these cases occurred throughout Nazi concentration camps during the Holocaust.[25] To guide its verdicts in the Nuremberg Doctors Trial in 1947, the court consulted the newly issued Nuremberg Code ("Code"), a ten-point code that sets forth the guidelines for human experimenta-

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20. For the complete text of the Oath, see http://www.sskrplaw.com/bioethics/oath.html (last visited Apr. 30, 2002) (on file with the Notre Dame Journal of Law, Ethics & Public Policy).

21. HIPPOCRATES, HIPPOCRATIC OATH (5th Cent. B.C.), *available at* http://www.sskrplaw.com/bioethics/oath.html (on file with the Notre Dame Journal of Law, Ethics & Public Policy).

22. *Id.*

23. *Id.* The Oath states, "I will not give [fatal drugs] to anyone if I am asked, nor will I suggest any such thing." *Id.*

24. For an outline of such cases, see Alan Milstein, BIOETHIC CHRONOLOGY: A HISTORY OF BROKEN RULES, *at* http://www.sskrplaw.com/bioethics/chronology.html (last visited Apr. 30, 2002) (on file with the Notre Dame Journal of Law, Ethics & Public Policy).

25. Some experiments included injecting Polish priests with Malaria, burning Russian prisoners with Phosphor to determine the best treatment for the scarring from Phosphor bombs and performing vivisection, or bone and muscle grafting, experiments on Polish women. DOCUMENT F 321, FOR THE INTERNATIONAL WAR COUNCIL AT NUREMBERG, THE COLLECTIVE "DAS LICHT"—(THE LIGHT), *available at* http://www.technologyartist.com/concentration camp/index.html (last visited Apr. 30, 2002) (on file with the Notre Dame Journal of Law, Ethics & Public Policy). Other such experiments are listed in Milstein, *supra* note 24.

tion.[26] The first sentence of the Code states, "[T]he voluntary consent of the human subject is absolutely essential."[27] The Code then sets forth the meaning of this mandate, stating:

> This means that the person involved should have the 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.*[28]

Unlike domestic informed consent laws, the Nuremberg Code applies to all research subjects, regardless of individual country regulations. The international community, however, never adopted the Code, leaving doubts as to whether it actually *binds* researchers in any country.[29]

2. The Roots of Informed Consent in the United States

Although the international community never adopted the 1949 Nuremberg Code as binding international law, U.S. courts began enforcing informed consent during the early 1900s. In 1908, Mary Schloendorff entered a New York hospital with a stomach disorder.[30] After finding a lump in her stomach, her physicians recommended an ether exam to determine the character of the lump.[31] Ms. Schloendorff consented to the ether exam, but specifically told her physicians that they should not operate.[32] The physicians performed the exam, and despite Ms. Schloendorff's instructions, operated to remove a tumor from

26. NUREMBERG CODE (1949), *available at* http://ohsr.od.nih.gov/nuremberg.php3 (on file with the Notre Dame Journal of Law, Ethics & Public Policy).

27. *Id.* ¶ 1.

28. *Id.* (emphasis added).

29. Dawn Joyce Miller, *Research and Accountability: The Need for Uniform Regulation of International Pharmaceutical Drug Testing*, 13 PACE INT'L L. REV. 197 (2001).

30. Schloendorff v. Soc'y of N.Y. Hosp., 105 N.E. 92 (N.Y. 1914).

31. *Id.* at 93.

32. *Id.*

her stomach at that time.[33] Ms. Schloendorff sued the hospital and physicians and, upon a verdict for the hospital, appealed the case to the Court of Appeals.[34]

While Ms. Schloendorff appealed the case on other grounds, it is better known for being the first to articulate the concept of informed consent. In his opinion, then-Judge Cardozo wrote, "[e]very human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation *without his patient's consent* commits an assault, for which he is liable in damages."[35]

Forty-three years later, a California appellate court gave the doctrine its name.[36] In *Salgo v. Stanford University*, Martin Salgo sued Stanford University after becoming permanently paralyzed following a diagnostic procedure at the University's hospital.[37] Mr. Salgo testified that he was not told of the nature of the procedure, including its details and possible risks.[38] In its discussion of the duty to disclose, the court stated:

> A physician violates his duty to his patient . . . if he withholds any facts that are necessary to form the basis of an intelligent consent by the patient to the proposed treatment. Likewise, the physician may not minimize the known dangers of a procedure or operation in order to induce his patient's consent. . . . [I]n discussing the element of risk a certain amount of discretion must be employed consistent with the full disclosure of facts necessary to an *informed consent*.[39]

Since then, the doctrine of informed consent has evolved into both a common law and a statutory doctrine, requiring physicians to disclose treatment risks and details to patients before administering a proposed treatment.

B. *The Current Doctrine*

Early informed consent cases in the United States took a battery approach, that is, that the injury resulted from unauthorized contact with the patient.[40] As in *Schloendorff*, plaintiffs would claim that they did not authorize the physician to perform the

33. *Id.*
34. *Id.*
35. *Id.* (emphasis added).
36. Salgo v. Stanford Univ., 317 P.2d 170 (Cal. Ct. App. 1957).
37. *Id.* at 173–75.
38. *Id.* at 181.
39. *Id.* (emphasis added).
40. MATTHEW BENDER & CO., TREATISE ON HEALTH CARE LAW § 17.01[1][a] (2001) [hereinafter HEALTH LAW TREATISE].

procedure either, as Ms. Schloendorff had done, by explicitly refusing such treatment, or because they did not authorize a procedure that held the risk that the physician did not disclose. Today, the informed consent doctrine generally takes a negligence approach, although plaintiffs can assert battery in some circumstances.[41] A negligence claim does not require the plaintiff to show that the physician intentionally treated the patient without the patient's informed consent. Instead, the plaintiff must prove three elements: 1) the physician had a duty to provide the information; 2) the physician breached that duty by not providing the relevant information; and 3) that breach proximately caused the patient's injury.[42]

1. The Physician's Duty

The first element, the physician's duty to provide certain information, focuses on what kind of information the physician should provide. Generally, the information that the physician should disclose can be broken into five categories: diagnosis, nature and purpose of the proposed treatment, risks and consequences, possible alternative treatments, and the risks and consequences of forgoing the proposed treatment.[43] Physicians generally disclose both the diagnosis and the nature and purpose of the proposed treatment, and will generally discuss the consequences of forgoing the proposed treatment with the patient.[44] The physician must disclose any recognized approach that provides reasonably feasible alternatives under the circumstances to satisfy the requirement of disclosing possible alternative treatments.[45]

The risks and consequences category represents the most litigated category of disclosure requirements.[46] A plaintiff in an informed consent case involving the risks and consequences cate-

41. Because battery is an intentional tort, the plaintiff claiming battery must show that the physician intentionally committed the act that caused the injury. Some situations in which the plaintiff may still assert battery are: a physician performs an operation even when the patient did not consent to the operation; a physician performs one type of operation, but the patient consented to another; a physician obtains conditional consent, but disregards the condition. Conditional consent may include, for example, a plaintiff consenting to a procedure only if the physician finds a malignancy. For a discussion of informed consent claims involving battery, see Orduno v. Mowry, 2001 Cal. App. LEXIS 2698 (Cal. Ct. App.).

42. BRYAN A. LIANG, HEALTH LAW & POLICY 29 (2000).

43. HEALTH LAW TREATISE, *supra* note 40, § 17.02[2].

44. *Id.* § 17.02[2][a], [b], [e].

45. *Id.* § 17.02[2][e].

46. *Id.* § 17.02[2][c].

gory generally claims that the patient would have forgone the treatment if the physician had disclosed the omitted information regarding the risk. The plaintiff, however, cannot reasonably require the physician to disclose all risks.[47] For example, a physician need not disclose risks that are so slight or insignificant that they do not merit disclosure, or risks that are commonly known.[48] Additionally, physicians do not need to disclose risks if they determine that they should withhold disclosure based on "therapeutic privilege" or if emergency circumstances require the physician to administer the treatment before obtaining the patient's consent.[49] Disclosure under the risks and consequences category requires the physician to determine which risks warrant disclosure. Today, states generally take one of two approaches to determining which risks the physician should disclose: the physician-centered approach and the patient-centered approach.

2. The Physician-Centered Approach

The physician-centered approach requires the physician to disclose material risks and benefits that a reasonable physician would disclose in similar circumstances.[50] This approach is consistent with medical malpractice claims in that it alleges that the physician departed from common practice among physicians generally.[51] The first case to articulate the approach, *Natanson v. Kline*,[52] stated that the physician's duty to disclose is limited to the information that a reasonable medical practitioner would disclose under the same or similar circumstances.[53] The physician-centered approach requires the plaintiff to bring expert witnesses to testify as to what a reasonable physician would disclose in those circumstances. The "reasonable physician" standard, however, does not account for the unique circumstances that are inherent in every physician's decision to disclose certain risks to a specific patient, and every patient's decision to undergo treatment based on the disclosed risks.

3. The Patient-Centered Approach

In 1972, a circuit court held, in *Canterbury v. Spence*, that physicians should determine whether to disclose certain information

47. *Id.*
48. *Id.*
49. LIANG, *supra* note 42, at 38, 40.
50. *Id.* at 29.
51. HEALTH LAW TREATISE, *supra* note 40, § 17.03[1][a].
52. 350 P.2d 1093 (Kan. 1960).
53. *Id.* at 1106.

based on the information that a *patient* would want to know in deciding whether to undergo the treatment, giving rise to the patient-centered approach.[54] This approach requires the physician to disclose material risks and relevant treatment alternatives that a patient would want to know to make an informed decision.[55] The approach is further divided into a subjective approach and an objective approach. The subjective approach asks whether the particular patient would have chosen to forgo the treatment had the physician disclosed the omitted information. This requires the plaintiff to show that the omitted information was so material to the patient's decision that the patient would have forgone the treatment had the information been disclosed. Because plaintiffs bring informed consent claims following injury, the subjective approach requires the plaintiff to show that even if the treatment had not resulted in injury, the patient still would have chosen to forgo the treatment.

The objective approach remedies the hindsight that the subjective approach requires. The objective approach asks whether a *reasonable* patient in similar circumstances would choose to forgo the treatment if the physician disclosed the omitted information. Thus, the approach does not require speculation as to whether a particular patient would have chosen to forgo the treatment, which requires knowing the patient's state of mind and unique circumstances and considerations.

In *Canterbury,* the court determined that a patient's right to self-determination "shapes the boundaries of the [physician's] duty to reveal."[56] The court further stated, "The scope of the physician's communications to the patient, then, must be measured by the patient's need, and that need is the information material to the decision."[57] The physician-based standard, the court determined, is flawed for two reasons. First, the court questioned whether a professional consensus requiring disclosures actually could exist in the medical community.[58] Circumstances unique to a particular situation could cause a physician to determine that disclosure would not be necessary, while the same physician may, in a different circumstance, determine that disclosure would be necessary for the patient to make an informed decision.[59] Second, the court determined that the physician-based approach ignores the patient's right to self-determination, and

54. Canterbury v. Spence, 464 F.2d 772 (D.C. Cir. 1972).
55. LIANG, *supra* note 42, at 30.
56. *Canterbury,* 464 F.2d at 786.
57. *Id.*
58. *Id.* at 783–84.
59. *Id.*

instead "bind[s] the disclosure obligation to medical usage [and arrogates] the decision on revelation to the physician alone."[60] Since *Canterbury*, approximately twenty-three states have adopted the patient-centered approach, while some continue to apply the physician-centered approach, and others have adopted neither a physician-centered nor a patient-centered approach.[61]

While there is still no consensus on which standard a court should use to determine whether a physician had a duty to disclose the omitted information, courts agree that the breach of the physician's duty is not adequate to establish the physician's liability.[62] The plaintiff must also show that the patient suffered an injury and that the injury resulted from the physician's nondisclosure. Showing that the patient would have forgone treatment, and thus would have escaped the resulting injury, had the physician disclosed the omitted information, generally shows causation.[63]

While informed consent in research parallels informed consent in clinical treatment, the unique circumstances of research call for special considerations in obtaining informed consent. Addressing this need, recent informed consent cases have expanded the doctrine beyond medical risks that are inherent in the procedure.

III. INFORMED CONSENT IN MEDICAL RESEARCH

A. *The* Moore *Decision*

In 1990, the California Supreme Court considered whether informed consent should extend to research and financial interests.[64] The plaintiff, John Moore, sought treatment for hairy-cell leukemia at the Medical Center of the University of California at Los Angeles ("UCLA Hospital").[65] He visited the UCLA Hospital strictly to treat his leukemia, and he did not agree to participate in research there.[66] His physician, however, discovered in the course of Moore's treatment, that Moore's cells could be extremely valuable in research.[67] During the course of Moore's

60. *Id.* at 784.
61. HEALTH LAW TREATISE, *supra* note 40, § 17.03[4].
62. *Id.* § 17.04.
63. *Id.*
64. Moore v. Regents of the Univ. of Cal., 793 P.2d 479 (Cal. 1990).
65. *Id.* at 480.
66. *Id.* at 481.
67. *Id.* The potential value of Moore's cells was a direct result of an overproduction of a protein called a lymphokine. Lymphokines are produced by certain white blood cells, called T-cells, and regulate the immune system. Some forms of this protein have potential therapeutic value. The genetic code

treatment, the physician and other defendants actively researched samples taken from Moore for the *sole purpose* of research, rather than treatment.[68] Eventually, the defendants developed and patented a cell line using Moore's cells.[69] During this time, the defendants concealed their research interests from Moore, leading Moore to believe that his physician performed every procedure for the purpose of treatment, when in fact some procedures only related to research.[70] Moore brought an action against the defendants for, among other things, lack of informed consent, alleging that the physician did not obtain Moore's consent to perform certain procedures because he was never told of the physician's research or financial interests in his cells.[71]

The court analyzed the informed consent issue based on the three principles of informed consent: adults of sound mind have the right, in exercising control over their bodies, to determine whether to submit to lawful medical treatment; the patient's consent to treatment must be an informed consent; and a physician has a fiduciary duty to disclose *all information* that would be material to the patient's decision.[72] The court recognized that most plaintiffs bringing informed consent cases allege that the physician failed to disclose a medical risk.[73] Despite this, however, the court determined that informed consent may extend to personal and financial interests, stating, "[A] physician must disclose personal interests unrelated to the patient's health, whether research or economic, that may affect the physician's professional judgment . . . ."[74] The court recognized that California law requires physicians to disclose some non-medical information in obtaining a patient's informed consent.[75] That information may

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responsible for producing the protein, if identified, can be used to produce large quantities of the protein in a lab. The genetic code, however, is extremely difficult to locate because the T-cells produce more than one type of this protein. Moore's T-cells overproduced certain of these proteins, making it easier to find the corresponding genetic code. These cells taken from Moore were used to develop a cell line, which is a cell culture that can reproduce indefinitely. Because most cell lines are difficult to develop, a successful cell line has a huge market potential. *Id.* at 481 n.2.

68. *Id.* at 481.
69. *Id.* at 482.
70. *Id.* at 481.
71. *Id.* at 482–83.
72. *Id.* at 483 (citing Cobbs v. Grant, 502 P.2d 1 (1972)).
73. *Id.*
74. *Id.*
75. *Id.*

include funding sources in research or referrals for which the physician stands to benefit.[76]

In determining that informed consent may extend to financial interests, the court discussed the competing roles of the physician in treatment and research. A physician who treats a patient recommends and performs certain procedures based on the potential benefit in relation to the potential risks.[77] The patient's needs represent the determining factor in medical treatment. A physician will not utilize treatment that does not stand to provide any material benefit to the patient. A *researcher*, however, seeks to use the patient to develop potentially beneficial treatments. In most research cases, the patient knows that the treatment is not fully developed. Patients understand that, while the treatment may provide no lasting value to them, other patients in the future may benefit from the knowledge gained during the research. Thus, the researcher is driven not by the patient's own needs, but by a research interest that may offer only marginal, if any, benefit to the patient.[78]

According to the *Moore* court, the physician who has a research interest in the patient may, consciously or unconsciously, take that interest into consideration in recommending certain procedures.[79] Thus, the physician has a duty to disclose certain outside interests so patients may determine their own course of treatment.[80] The court held that these outside interests include "personal interests unrelated to the patient's health, whether research or economic, that may affect [the physician's] medical judgment."[81]

While the *Moore* court determined that a physician should disclose financial conflicts in the patient consent form, the court considered only disclosures where patients are not actually aware of research interests in their treatment. Patients agreeing to participate in medical research are aware of a research interest in their treatment. In fact, many patients participate in research because that research presents the best hope for successful treatment.

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76. *Id.* at 484 (citing BUS. & PROF. § 654.2, and HEALTH & SAFETY § 24176).

77. *Id.*

78. *Id.*

79. *Id.*

80. *Id.*

81. *Id.* at 485.

B. *The Belmont Report*

Before *Moore*, Congress, addressing the need for basic ethical principles underlying human subject research, signed the National Research Act into law,[82] which created the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research ("Research Commission").[83] In response to its charge to develop guidelines to follow to ensure that researchers apply those basic ethical principles to biomedical research, the Research Commission issued the Belmont Report.[84] Rather than establishing specific recommendations, the Research Commission set to provide guidelines that would create a framework for determining the ethical course of action in resolving specific ethical problems and would not be outdated by advances in medicine that otherwise may not fall under more specific recommendations.[85] The Belmont Report establishes three ethical principles as the underlying principles in human subject research: Respect for Persons, Beneficence, and Justice.[86]

1. Respect for Persons

The first category, Respect for Persons, incorporates two ethical beliefs: that individuals are autonomous and that those individuals with diminished autonomy should be protected.[87] The first belief, that individuals are autonomous, requires acknowledging that people are capable of deliberating decisions and acting upon their deliberations.[88] To respect that autonomy is to allow the individual to make those choices without obstructing those choices unless they may harm others.[89] To show a lack of respect for the individual's autonomy is to "repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to *withhold information* necessary to make a considered judgment, when there are no compelling reasons to do so."[90] Thus, Respect for Persons requires that research subjects enter into the research both vol-

82. National Research Act, Pub. L. No. 93-348, 88 Stat. 342 (1974).
83. *Id.* § 201, 88 Stat. 348.
84. NAT'L COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS IN BIOMEDICAL AND BEHAV. RES., THE BELMONT REPORT (1979), *available at* http://ohsr.od.nih.gov/mpa/belmont.php3 (on file with the Notre Dame Journal of Law, Ethics & Public Policy) [hereinafter BELMONT REPORT].
85. *Id.*
86. *Id.*
87. *Id.* pt. B-1.
88. *Id.*
89. *Id.*
90. *Id.* (emphasis added).

untarily and with sufficient information. In determining whether certain information is necessary to an informed consent, the Belmont Report suggests that researchers use a variation of the reasonable patient standard,[91] the standard of the "reasonable volunteer."[92] The reasonable volunteer standard allows patients to consider the issues that are important to a fully informed choice to participate in research, while acknowledging an awareness that the research may not be beneficial to them, and, in fact, may not be fully understood.[93]

2. Beneficence

The second principle, Beneficence, requires that researchers and research institutions engage in efforts to secure the well being of the research subjects.[94] While the Belmont Report acknowledges that the term "Beneficence" generally refers to acts of kindness or charity that exceed strict obligation, Beneficence in medical research is itself a strict obligation.[95] That obligation encompasses two requirements, avoiding harm and maximizing benefits while minimizing risks.[96] While those tasks fall to researchers and research institutions, the Belmont Report charges society at large with the obligation to recognize both the long-term benefits and risks that may result from medical research.[97] Society's recognition of the long-term risks and benefits that may result from medical research allows communities to hold institutions and lawmakers accountable for practices and policies that protect patients. As a result, an informed society will ensure that the law adjusts to changes in the research environment.

3. Justice

The Belmont Report recognizes the final ethical principle in medical research as Justice, or "[w]ho ought to receive the benefits of research and bear its burdens[.]"[98] Thus, an injustice occurs when one person is wrongfully denied a benefit or unduly bears a burden. Recognizing a commitment to Justice, institutions must consider whether one group bears a burden without reaping the benefits or whether a particular group bears an

91. *See supra* notes 54-63 and accompanying text.
92. BELMONT REPORT, *supra* note 84, pt. C-1.
93. *Id.*
94. *Id.* pt. B-2.
95. *Id.*
96. *Id.*
97. *Id.*
98. *Id.* § B(3).

entire burden, when the benefit spreads beyond that group.[99] For instance, the Belmont Report identifies the Tuskegee syphilis study, where researchers studied one particular population, even when that disease was not restricted to that population.[100]

4. Application

In discussing the three ethical principles, as well as placing issues in research within those principles, the Research Commission recognized that adhering to one principle does not make research ethical.[101] Instead, researchers and research institutions must consider each principle in planning and implementing research. Thus, while the Commission recognizes informed consent as an important, and even necessary, component of ethical research, even perfect disclosure will not ensure ethical research.[102]

C. *The Declaration of Helsinki*

While the Belmont Report recognized the need for patient protection in the United States, the World Medical Association, recognizing patient protection as a world-wide need, issued the Declaration of Helsinki in 1964.[103] The Declaration of Helsinki ("Declaration"), like the Nuremberg Code, is an international document, which does not carry legal effect in the international community. Unlike the Nuremberg Code, however, the Declaration does carry effect within the international medical community, and has been amended several times, most recently in 2000, to reflect the changing medical research environment.[104] The Declaration sets forth legal principles that members of the World Medical Association must follow in engaging in medical research involving human subjects. It not only addresses the basic principles of medical research, but also instances, as in *Moore*, in which physicians combine medical research with medical care.[105]

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99. *Id.*

100. *Id.* During the 1940s, U.S. researchers studied the untreated course of syphilis on poor, rural, African-American men, even though syphilis was not confined to that particular population. *Id.*

101. *Id.*

102. *Id.*

103. WORLD MED. ASSOC., DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS, (1964, amend. 2000), *available at* http://www.wma.net/e/policy/17-c_e.html (on file with the Notre Dame Journal of Law, Ethics & Public Policy) [hereinafter DECLARATION OF HELSINKI].

104. *Id.*

105. *Id.*

The Declaration acknowledges that medical advancement relies on research that ultimately involves human subjects.[106] Acknowledging the value of human research, however, the Declaration requires the researcher-physician to assess the predictable risks and burdens and compare them to the foreseeable benefits to both the patient and others.[107] The Declaration's impact on medical research, however, is not that it requires informed consent, but that it requires that researchers submit research plans, or protocols, to an independent ethical review committee.[108] The United States refers to these committees as "Institutional Review Boards" ("IRBs"). The Declaration requires that the IRB approve research protocols according to the laws and regulations of the country in which the research is performed.[109] In addition, the IRB has the right to monitor ongoing trials.[110] In that regard, the Declaration requires the researcher to provide monitoring information to the IRB, "especially any serious adverse events."[111] Finally, the Declaration requires that the researcher inform the IRB of "information regarding funding, sponsors, institutional affiliations, *other potential conflicts of interest* and incentives for subjects."[112]

D. *The Institution's Role in Disclosure Determinations: Institutional Review Boards*

In 1974, following guidelines set forth in the Declaration of Helsinki, the Department of Health, Education, and Welfare promulgated regulations establishing IRBs.[113] IRBs in the United States are charged with overseeing and approving research protocols for research involving human participants.[114] Each IRB is responsible for protecting the rights of those participants, both before the research commences and during the

106. *Id.* ¶ A(4).

107. *Id.* ¶ B(16). This requirement, the Declaration states, does not necessarily preclude research on healthy participants.

108. *Id.* ¶ B(13).

109. *Id.*

110. *Id.*

111. *Id.*

112. *Id.* (emphasis added).

113. OFFICE FOR HUMAN RESOURCE PROTECTIONS, INSTITUTIONAL REVIEW BOARD GUIDEBOOK (1993), *available at* http://ohrp.osophs.dhhs.gov/irb/irb_guidebook.htm (on file with the Notre Dame Journal of Law, Ethics & Public Policy) [hereinafter IRB GUIDEBOOK]; IRB regulations are codified at 21 C.F.R. § 56 (FDA requirements), and 45 C.F.R. § 46 (HHS requirements). For further discussion of the FDA and HHS requirements, see *infra* notes 118–127 and accompanying text.

114. IRB GUIDEBOOK, *supra* note 113, ch. I(A).

research period.[115] The IRB is an institutional body, and each research institution must establish at least one IRB to review its research protocols.[116] Alternatively, an institution can submit its protocols to another institution's IRB for review.[117]

1. Government Regulation of IRBs

Both the Food and Drug Administration ("FDA") and the Department of Health and Human Services ("HHS") regulate human research in general, and IRBs in particular. As a result, there is no uniform standard to apply to IRB evaluations of research protocols. FDA and HHS requirements are substantially similar, however, making compliance with both FDA and HHS regulations relatively simple. The regulations apply to different types of research: HHS regulations apply to research involving human subjects that is supported either entirely or partially by HHS or conducted by HHS.[118] FDA regulations, on the other hand, apply to all research involving products that the FDA regulates, including research and marketing permits for drugs.[119] Research that is subject to both HHS and FDA regulations must meet both sets of regulations.[120]

2. IRB Membership

Both the FDA and HHS require that IRBs include at least five members, although the IRB need not limit the number of members.[121] The membership should reflect varying backgrounds, and IRB members should possess qualifications through experience and expertise to safeguard the rights of the human subjects.[122] Additionally, the laws regulating IRBs recognize the unique needs of each research institution, medical community, and the community surrounding the institution. In appointing members, IRBs should take these factors into consideration.[123] Both FDA and HHS regulations state:

> The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the

115. *Id.*
116. *Id.* ch. I(B).
117. *Id.*
118. HHS Policy for Protection of Human Subjects, 45 C.F.R. § 46.101 (2001).
119. Institutional Review Boards General Provisions, 21 C.F.R. § 56.101 (2001).
120. IRB GUIDEBOOK, *supra* note 113, ch. II(B).
121. 21 C.F.R. § 56.107(a); 45 C.F.R. § 46.107(a).
122. 21 C.F.R. § 56.107(a); 45 C.F.R. § 46.107(a).
123. 21 C.F.R. § 56.107(a); 45 C.F.R. § 46.107(a).

> members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.[124]

While IRB guidelines require expertise, members of only one profession cannot compose an IRB's entire membership.[125] In that regard, the IRB must include at least one member whose primary concern involves scientific considerations and one whose considerations are primarily non-scientific.[126] To assure independence, at least one member must be independent of the research institution.[127] The IRB should draw the independent member from the institution's community at large.[128] Possible members include lawyers, who possess familiarity with laws regulating the institution, or ministers, who are familiar with ethical and religious considerations in the community.[129] Regardless of the member's profession, that person should be knowledgeable about the local community, and willing and able to discuss the proposed research from that perspective.[130] Additionally, the IRB should ensure that the community member is not subject to intimidation by the IRB's non-independent members.[131]

3. IRB Protocol Review

Generally, any research involving human subjects must be submitted to the IRB for approval. This is called "protocol review." Research exempted from IRB approval includes educational testing, surveys in which the researcher will record no identifying information that can link the subjects to the data, and research involving existing data or specimens where the researcher will record no data that can link the subject to the information or specimen.[132] In reviewing research protocols, the IRB should consider the principal investigator's qualifications, the protocol's risks versus benefits to both the subjects and society, and whether the informed consent procedure is adequate.[133]

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124. 21 C.F.R. § 56.107(a); 45 C.F.R. § 46.107(a).
125. 21 C.F.R. § 56.107(b); 45 C.F.R. § 46.107(b).
126. 21 C.F.R. § 56.107(c); 45 C.F.R. § 46.107(c).
127. 21 C.F.R. § 56.107(d); 45 C.F.R. § 46.107(d).
128. IRB GUIDEBOOK, *supra* note 113, ch. I(B).
129. *Id.*
130. *Id.*
131. *Id.*
132. 45 C.F.R. § 46.101(b).
133. IRB GUIDEBOOK, *supra* note 113, ch. I(C) (qualifications), ch. III(A) (risk/benefit analysis), ch. III(B) (informed consent).

Consideration of the principal investigator's qualifications should include the investigator's professional development and the related degree of the protocol's complexity and risk to the subjects.[134] Researchers must submit their protocols to the IRB, including provisions for the protection of research subjects and sample informed consent documents.[135] The researcher, however, is not required to submit documentation of potential conflicts of interest, including financial conflicts of interest.

4. Risk/Benefit Analysis

After reviewing the research protocol, the IRB must perform a risk/benefit analysis. The anticipated benefits to the research subjects or society must justify the accompanying risks posed to the subjects from their participation.[136] Following the "reasonable volunteer" standard,[137] the IRB must evaluate the risks based on the conditions that make the research dangerous to the subject per se, not based on the chances that specific individuals are willing to undertake to achieve their goals.[138] The IRB must then determine whether the anticipated benefit justifies asking *any* person to take that risk.[139]

In determining whether an anticipated benefit outweighs a risk, the IRB must identify and assess the risks, determine whether it can minimize the risks as much as possible, identify the anticipated benefits, determine whether those benefits outweigh the risks, assure that the subjects will be given an accurate description of the risks, and determine how often the IRB should review the investigation during the course of the research.[140]

In identifying and assessing the risks, the IRB should consider physical, psychological, social, and economic risks.[141] Physical harms include exposure to minor pain, discomfort or injury from medical procedures, and possible side effects of drugs.[142] Psychological harms include changes in thought processes or emotions.[143] Those harms also encompass stress and feelings of guilt, which generally result from behavioral research.[144] Addi-

134. *Id.*
135. *Id.*
136. *Id.* ch. III(A).
137. *See supra* notes 91-93 and accompanying text.
138. IRB GUIDEBOOK, *supra* note 113, ch. III(A).
139. *Id.*
140. *Id.*
141. *Id.*
142. *Id.*
143. *Id.*
144. *Id.*

tionally, the IRB may consider invasion of privacy and breach of confidentiality as psychological harms.[145] Likewise, breach of confidentiality may result in social or economic harms because it could lead to embarrassment within a subject's business or social group or in criminal prosecution.[146] IRBs should be particularly sensitive to information regarding drug abuse, mental illness, illegal activities or sexual behavior, or behavioral research that may "label" or stigmatize the subjects, resulting in social or economic harms.[147] To the extent that the IRB determines that the protocol does present these risks to the subjects, the IRB should assure that those risks are minimized without negatively affecting the integrity of the research. Despite its extensive role, however, the IRB is not responsible for determining whether a conflict of interest may result in additional risks to the subjects.

5. Disclosure Determinations

Following its assessment of the risks, the IRB must then determine whether subjects are adequately informed of those risks when the researchers obtain informed consent. In determining whether the informed consent process is adequate, the IRB should consider "that informed consent is an ongoing process, not a piece of paper or a discrete moment in time."[148]

HHS regulations require that certain information be provided to research subjects in obtaining informed consent.[149] That information includes an explanation of the purposes and duration of the research,[150] a description of reasonably foreseeable risks,[151] a description of the benefits to the subject or others that are reasonably expected as a result of the research,[152] a disclosure of alternative treatments that may be available to the subject,[153] a disclosure of the measures the institution will take to preserve the patient's confidentiality,[154] a description of any compensation or treatment that is available should the patient suffer injury as a result of a risk,[155] the names of people or institutions the subject can contact to answer additional questions or

145. *Id.*
146. *Id.*
147. *Id.*
148. *Id.* ch. III(B).
149. HHS Policy for Protection of Human Research Subjects, 45 C.F.R. § 46.116(a) (2001).
150. *Id.* § 46.116(a)(1).
151. *Id.* § 46.116(a)(2).
152. *Id.* § 46.116(a)(3).
153. *Id.* § 46.116(a)(4).
154. *Id.* § 46.116(a)(5).
155. *Id.* § 46.116(a)(6).

if the subject suffers an injury,[156] and a statement that participation in the research is voluntary and that the subject may discontinue participation at any time.[157]

HHS does not require that the researcher disclose any conflicts of interest, including financial conflicts, in obtaining informed consent. The IRB, however, may determine that investigators should disclose certain other information. The IRB Guidebook requires the IRB to take the patient-centered approach to those disclosures, stating that "the IRB should attempt to view the matter from the subject's perspective by asking what facts the subjects might want to know before deciding whether or not to participate in the research."[158] As the Gelsinger and Hutch cases illustrate,[159] IRB approval and review of research protocols does not shield research teams and institutions from allegations of misconduct, particularly as those allegations relate to financial conflicts of interest. Current institutional responses to those allegations, however, address the need for an IRB's awareness of and focus on those conflicts of interest.

IV. Responses to Criticisms and Concerns

A. *Institutional Responses: The Hutch's Response*

In March 2001, in response to criticisms related to its policy regarding financial conflicts of interest,[160] the Hutch formed a committee, called the Committee for Patient Protection in Research Trials ("Patient Protection Committee"), to review its policies and procedures. The Patient Protection Committee's review included a review of the Hutch's two IRBs, its informed consent process, and its conflict of interest and financial disclosure policies.[161] In reviewing these areas, the Patient Protection Committee consulted independent reviewers, who are considered experts in their fields, to submit reports and recommendations after extensively studying the Hutch's policies.[162]

In submitting its findings, the Patient Protection Committee called particular attention to the Hutch's financial conflict of interest policy, recommending that the Hutch institute an outright ban on all financial conflicts of interest.[163] The Hutch later

156. *Id.* § 46.116(a)(7).
157. *Id.* § 46.116(a)(8).
158. IRB Guidebook, *supra* note 113, ch. III(B).
159. *See supra* notes 2–18 and accompanying text.
160. *See supra* note 18 and accompanying text.
161. Hutch Patient Protection Report, *supra* note 1, § II.
162. *Id.*
163. *Id.* § III(A)(2)(a).

adopted those recommendations.[164] The independent reviewer's report on conflicts of interest and financial disclosure policies, however, sets forth a less drastic standard that allows researchers to maintain those financial interests while assuring patient protection.[165] The independent reviewer's report recommended implementing a policy requiring investigators with financial interests totaling more than $8,000 from one company per year, to disclose those interests in their publications and presentations.[166] Additionally, the report recommended that investigators with financial interests related to their research disclose those interests to their colleagues.[167] Presumably, this disclosure would cause the investigator's peers to scrutinize the investigator's work should questions arise regarding independence. Next, the report recommended that the Hutch consider *all* equity interests in privately held companies significant financial interests, regardless of the current value of the company.[168] Recognizing the role of IRBs in reviewing financial conflicts of interest, the report additionally recommended that the IRB review financial conflicts in studies annually, rather than solely at a study's initial review.[169]

In reviewing the policies and procedures of the Hutch's IRBs and informed consent process, the independent reviewers departed from the Committee's recommendation of an outright ban on financial conflicts of interest. The reviewers recommended that the *Hutch* manage financial conflicts of interest, not its IRBs, and that researchers should *not* disclose financial conflicts to patients in obtaining informed consent, stating that "[s]ick patients who are contemplating enrollment in clinical

164. FRED HUTCHINSON CANCER RES. CENTER BD. OF TRUSTEES, PATIENT PROTECTION OVERSIGHT COMMITTEE PROGRESS REPORT (2002), *at* http://www.fhcrc.org/response/patientprotection/ppoc_report_2002.pdf (on file with the Notre Dame Journal of Law, Ethics & Public Policy).

165. *See* Margaret L. Dale, REVIEWER REPORT ON CONFLICT OF INTEREST AND FINANCIAL DISCLOSURE, *at* http://www.fhcrc.org/response/patientprotection/att_d.pdf (last visited Oct. 13, 2002) (on file with the Notre Dame Journal of Law, Ethics & Public Policy) [hereinafter DALE REPORT].

166. *Id.* at 11.

167. *Id.*

168. *Id.* The Hutch's policies regarding financial conflicts of interest as of the date of the Dale Report restricted Hutch representatives from participating in transactions involving the Hutch if the representative, or a member of the representative's family, had or would receive a significant economic interest, or if the transaction involved a business in which the representative, or a member of the representative's family, had or would receive a significant economic interest. HUTCH PATIENT PROTECTION REPORT § II(D).

169. DALE REPORT, *supra* note 165, at 12.

research are usually not in a position to weigh the significance of financial disclosure issues relative to their care."[170]

B. *Government Response: The Office of Human Research Protection*

Recognizing the need for uniform guidelines, in January 2001, the Office of Human Research Protection ("OHRP"), a division of HHS, issued its Draft Interim Guidance regarding financial conflicts of interest in human research.[171] Responding to issues raised in the Gelsinger case[172] and to five new initiatives to strengthen human subject research protection, announced by then-Secretary of Health and Human Services, Donna Shalala, in May 2000, the OHRP set forth guidelines for responding to, minimizing, and disclosing financial incentives ("Draft Interim Guidance"). The guidelines address five areas: institutional considerations, clinical investigators, IRB members, IRB review of protocols, and consent documents and informed consent.[173]

1. Institutional Financial Conflicts of Interest

In addressing institutional considerations, the OHRP noted that not only do representatives of the institutions possess financial conflicts of interest, but, increasingly, the institution itself possesses those conflicts, often in the form of agreements with corporations that benefit both entities.[174] Those conflicts may directly influence how an institution conducts a trial, including how it enrolls subjects, how it reports adverse events, and how it evaluates trial data.[175] Noting that many institutions have already established a Conflict of Interest Committee, the OHRP determined that institutions should actively gather information regarding conflicts of interest and submit that information to both the Conflict of Interest Committee and the institution's IRB.[176] Because institutions often possess significant financial interests in research, the OHRP suggested that IRBs, as institu-

170. ERNEST PRENTICE & GWENN OKI, REVIEWER REPORT ON INSTITUTIONAL REVIEW BOARD AND INFORMED CONSENT PROCESS 15, *at* http://www.fhcrc.org/response/patientprotection/att_b.pdf (June 1, 2001) (on file with the Notre Dame Journal of Law, Ethics & Public Policy) [hereinafter PRENTICE/OKI REPORT].

171. OFF. FOR HUM. RES. PROTECTIONS, DRAFT INTERIM GUIDANCE (2001), *available at* http://ohrp.osophs.dhhs.gov/nhrpac/mtg12-00/finguid.htm (on file with the Notre Dame Journal of Law, Ethics & Public Policy) [hereinafter DRAFT INTERIM GUIDANCE].

172. *See supra* note 2 and accompanying text.

173. DRAFT INTERIM GUIDANCE, *supra* note 171.

174. *Id.* § 1.6.

175. *Id.*

176. *Id.* § 1.1.

tional entities, may be subject to institutional pressures to approve protocols, turning a blind eye to financial conflicts of interest.[177] To prevent institutional pressures, IRB members from outside of the institution, with no financial relationships to the institution, should actively participate in the review process.[178]

2. The Investigator's Financial Conflicts of Interest

IRB members should be aware of, and actively review, any financial conflicts that the institution or its clinical investigator may have. The Draft Interim Guidance sets forth policies that institutions and IRBs should employ when clinical investigators have financial conflicts.[179] In determining whether an investigator's financial interests present a conflict, the IRB should consider whether the relationship leads the investigator to prefer one outcome over another.[180] As the Draft Interim Guidance states, "Influenced by a financial incentive, an investigator may, even if unwittingly, color the [informed] consent discussion in a manner that encourages participation by subtly minimizing the presentation of risks or overstating the benefits."[181] Should an investigator and a sponsor enter into a financial agreement, the Draft Interim Guidance recommends that the institution's Conflict of Interest Committee review the agreement.[182] If the Conflict of Interest Committee determines that the researcher cannot avoid the conflict, it should determine how to best reduce and manage the conflict, and share that determination with the institution's IRB for consideration during its review of the protocol.[183] The IRB members, in addition, should determine whether they have any potential financial conflict of interest related to the protocols they review.[184] Members who determine that they possess a potential financial conflict of interest in a particular protocol should withdraw from review of that protocol.[185]

3. Review of Protocols Involving Financial Conflicts

The Draft Interim Guidance next sets forth criteria that the IRB should employ when considering financial conflicts of inter-

177. *Id.* § 1.3.
178. *Id.*
179. *Id.* § 2.
180. *Id.* § 2.1.
181. *Id.*
182. *Id.* § 2.2.
183. *Id.*
184. *Id.* § 3.1.
185. *Id.*

est in reviewing protocols.[186] When the IRB determines that a financial conflict of interest exists, and that the conflict cannot be eliminated, the Draft Interim Guidance advises the IRB to consider modifying the consent form to reflect the financial conflict.[187] Finally, the Draft Interim Guidance advises that, when an investigator's financial conflict of interest cannot be eliminated, the investigator "should not be directly engaged in aspects of the trial that could be influenced inappropriately by that conflict. These could include: the design of the trial, monitoring the trial, obtaining the informed consent, adverse event reporting, or analyzing the data."[188] In those instances, the Draft Interim Guidance recommends that the consent document disclose the financial conflict, including the financial arrangement and how the institution plans to manage it.[189]

C. *Government Response: Human Research Subject Protections Act of 2002*

In May 2002, Representative Diana DeGette introduced the Human Research Subject Protections Act of 2002 ("2002

186. *Id.* § 4.

187. *Id.* § 4.3. In determining whether and how to modify the consent form, the draft interim guidance suggests that the IRB consider the following questions:

1. Who is the sponsor?
2. Who designated the clinical trial?
3. Who will analyze the safety and efficacy data?
4. Is there a Data Safety Monitoring Board (DSMB)?
5. What are the financial relationships between the Clinical Investigator and the commercial sponsor?
6. Is there any compensation that is affected by the study outcome?
7. Does the Investigator have any proprietary interests in the product including patents, trademarks, copyrights, and licensing agreements?
8. Does the Investigator have equity interest in the company—publicly held company or non-publicly held company?
9. Does the Investigator receive significant payments of other sorts? (e.g., grants, compensation in the form of equipment, retainers for ongoing consultation, and honoraria)
10. What are the specific arrangements for payment?
11. Where does the payment go? To the Institution? To the Investigator?
12. What is the payment per participant? Are there other arrangements?

Id.

188. *Id.* § 4.4.

189. *Id.* § 5.3.

Research Act") into the House of Representatives.[190] Prior to the bill's introduction, many journalists focused their attention on the issue of the protection of research subjects.[191] The bill, however, which calls for reform in the very industry the journalists criticized, received little recognition after its introduction.[192] Despite the bill's lack of recognition, it calls for many of the same changes that journalists and patient advocates recommended in their criticisms of current practice rules. The bill calls for the harmonization of FDA and HHS regulations, establishes the subject's legal right to informed consent and provides guidelines for disclosure, and better defines the roles and requirements of IRBs.[193]

1. Uniform Regulations

Current regulations of human subject research vary widely. The regulations vary based on the sponsor, the type of institution conducting the research, the type of research, and even the population of research subjects.[194] HHS and FDA regulations do not always provide consistent guidance.[195]

The 2002 Research Act requires a review of those inconsistencies and, where possible, harmonization of the regulations.[196] Understanding that issues involved in human subject research may be unique to either FDA or HHS research, the 2002 Research Act allows for differences in the regulations only when they are necessary to reflect those issues, whether legal or factual, that are unique to research under only one set of regulations.[197] While the 2002 Research Act does not limit the issues that must undergo review for harmonization, it does require review of some specific issues, including regulations of significant financial

190. Human Research Protections Act of 2002, H.R. 4697, 107th Cong. (2002).

191. *See* Michael D. Lemonick & Andrew Goldstein, *At Your Own Risk*, TIME, Apr. 22, 2002, at 46 (cover story), *and* Duff Wilson & David Heath, *Uninformed Consent: What Patients At 'The Hutch' Weren't Told About Experiments In Which They Died*, SEATTLE TIMES, Mar. 11–15, 2001 (investigative report, Pulitzer Prize nominee).

192. One special report, published in August 2002, briefly mentions the bill. Tom Abate, *Experiments On Humans: Rules for Clinical Trials Are Confusing, Inconsistent; No Single Agency Regulates Medical Research On Humans*, S.F. CHRON., Aug. 5, 2002, at A1.

193. H.R. 4697, §§ 2, 3.

194. *See* Tom Abate, *supra* note 192. Criticizing this variation in regulations, some critics assert that rules regulating research on monkeys are more consistent than the rules that regulate research on humans.

195. *See supra* notes 118–59 and accompanying text.

196. H.R. 4697, § 2.

197. *Id.*

interests and requirements for a researcher's confirmation of the protection of the research participants.[198] The 2002 Research Act, however, does not provide any guidance on whether the regulations should favor or discourage financial conflicts of interest, instead leaving that determination to the HHS Secretary.

2. Informed Consent

While the current informed consent doctrine evolved from case law, and statutory provisions for informed consent left many issues to the physician's discretion, the 2002 Research Act sets forth the specific information that a clinical investigator must disclose when obtaining informed consent.[199] That information includes *any* conflict of interest the investigators have.[200] Interestingly, the bill requires the informed consent disclosures to include *any* conflicts of interest, which arguably prevents researchers from exercising their own judgment regarding whether a particular conflict is too insignificant to disclose.

3. Institutional Review Boards

The 2002 Research Act pays particular attention to IRBs. It sets forth membership requirements and requires continuing education for IRB members, provisions for situations in which an IRB member either has, or appears to have, a conflict of interest regarding research submitted to the IRB, and a review of a clinical investigator's conflict of interest.[201]

In contrast to current IRB membership requirements, the 2002 Research Act requires at least two members who possess scientific expertise and two members whose primary expertise relates to non-scientific areas.[202] The 2002 Research Act, however, provides that these requirements represent minimum numbers, and scientific experts should each compose at least twenty-five percent of the IRB's membership, while non-scientific

198. *Id.* The other differences required to undergo review are the provisions for research that relates to emergency intervention and the definition of "institution," which may determine how the regulations apply to a particular study. *Id.*

199. *Id.*

200. *Id.* Other information includes, but is not limited to: the purpose of the research; potential risks and benefits of participating in the research; the difference, if any, between the research and other therapeutic treatment; a statement giving the participant the right to leave the study at any time; the identity of the research sponsors; and any tests or procedures that are part of the research. *Id.*

201. *Id.*

202. *Id.*

experts should compose no less than twenty percent of the total membership.[203] In addition, at least two IRB members, but no less than twenty percent of the IRB's members, should include members who do not affiliate with the particular institution.[204] The Act provides, however, that the same person can satisfy both the non-scientific expert requirement and the non-affiliation requirement for purposes of satisfying the Act's requirements.[205]

In addition to altering an IRB's membership requirements, the 2002 Research Act creates provisions for continuing education of IRB members and for situations involving conflicts of interest.[206] Recognizing the importance of an IRB's sensitivity to ethical issues involved in certain types of medical research, the 2002 Research Act requires institutions to develop orientation programs for new IRB members and continuing education programs for existing IRB members, including a continuing education program with respect to ethical issues that relate to the particular research the IRB reviews.[207] Presumably, those continuing education programs could serve to educate IRB members in issues specific to the type of research they review, including risks associated with conflicts of interest. The 2002 Research Act provides for reporting such conflicts of interest. In the case of an IRB member with a conflict of interest, the 2002 Research Act requires the member to report that conflict to the institution, while the institution should report any institutional or investigator conflicts of interest to the IRB.[208] Interestingly, the 2002 Research Act does not create different reporting requirements for real versus perceived conflicts of interest, indicating that a *perceived* conflict of interest, even in the absence of a true conflict of interest, merits the same attention as a real conflict of interest.[209] Those conflicts of interest may include an IRB member's involvement as an investigator in the research, any proprietary

203. *Id.*

204. *Id.* Affiliation includes immediate family members of anybody who is affiliated with the institution, or any person who can identify a conflict of interest. *Id.*

205. *Id.* In addition to the general membership requirements, when an IRB reviews a proposal for research designed to include either a "vulnerable population" or a significant minority population, the IRB must include in its membership a representative of that particular population. *Id.* "Vulnerable populations" include the children, pregnant women, the mentally ill, prisoners, and the economically or educationally disadvantaged. HHS Protection of Human Subjects, 45 C.F.R. § 46.111 (2001).

206. H.R. 4697, § 2.

207. *Id.*

208. *Id.*

209. *Id.*

interests in the research, or any direct financial relationships or arrangements with a study's private sponsor.[210] If IRB members report their own conflicts of interest, the 2002 Research Act requires them to excuse themselves from IRB review of that particular study.[211] While the 2002 Research Act does not ban conflicts of interest, it does require an institution to seek to reduce or eliminate and oversee any perceived or real conflicts.[212]

V. RECOMMENDATIONS

Although the 2002 Research Act addresses many of the concerns articulated by patient advocates, among others, it does not address the concerns relating to an IRB's effectiveness. Allegations of misconduct, whether due to financial conflicts of interest or not, raise questions of the effectiveness of IRB review. While IRBs currently act to ensure the safety of clinical trials, regulations, time constraints, and internal pressures limit their effectiveness. To remedy those limitations, changes within institutions and the research industry and changes in the law should delegate a more active and independent role to IRBs, as well as establish more government oversight of research compliance. Increasing the effectiveness of IRBs, and decreasing misconduct in clinical research, requires, at the outset, three fundamental changes that will provide a foundation for future regulations and that can adapt to changes in technology and the research industry. First, both institutions and government organizations should strive to strengthen the role of IRBs. Next, the government should establish an oversight body to promulgate and enforce rules regarding clinical research. Finally, *all* clinical research should fall under those rules. These recommendations, while broad in scope, will provide a basis for better regulation of clinical research and improve overall confidence in medical research.

A. *Strengthen the Role of IRBs*

IRBs, which by law interact with individual research institutions and clinical trials, represent the best available opportunity to recognize and prevent research misconduct. Because researchers and research institutions must present proposed studies to IRBs for approval before the study can commence, IRBs have the opportunity to prevent research that represents too great of a risk, or can ensure that researchers and institutions

210. *Id.*
211. *Id.*
212. *Id.*

put adequate safeguards into place to prevent serious harm to research subjects. Unlike a government agency, an IRB can take a proactive role, by identifying potential problems *before* they occur. A government agency, on the other hand, if charged with the same task as an IRB, could potentially be stretched too thin, thus only able to identify problems *after* they occur, when an institution reports the problem to the agency. Currently, however, the law does not assure effective IRB review. Institutions and their review boards can strengthen the role of IRBs by ensuring complete independence, continuous monitoring, a relative reduction in the IRBs workload, and establishing a Conflicts of Interest Committee at each institution. These steps will allow the IRB to successfully implement recommendations such as those in the Draft Interim Guidance.

1. IRBs Should Be Completely Independent of Institutions

The current law requires that at least one IRB member be completely independent of the institution, while the 2002 Research Act modifies that requirement. An IRB with the legal minimum of five members, then, would easily outnumber the independent members representing a minority of the board, creating potential conflicts of interest within the IRB itself. As a result, the very committee that should protect patients from the harm that can result from conflicts of interest may sacrifice its own objectivity in its review of clinical trials. An *independent* institutional review board, on the other hand, whose independent members possess both scientific and non-scientific backgrounds, compose at least 50% of the IRB's membership, and which represents the community at large, not only presents the *image* of objectivity, but also can be *truly* objective in reviewing research protocols.

2. IRBs Should Engage in Continuous, Interactive Monitoring

While the law currently charges IRBs with continuous monitoring of clinical research, in reality IRBs often, if they do engage in continuous monitoring, merely monitor paperwork submitted by research team members. A policy that requires IRBs to engage in interaction with research team members and patients, as well as monitor paperwork submitted by the research team, will alert an IRB to potential problems that may arise during the course of the research. Likewise, a policy that encourages this interaction will convey an institution's commitment to both compliance with the law and patient protection, thus building patient

and community trust in the integrity of the research and the institution.

3. An IRB's Workload Should Be Reduced

Finally, to implement a policy that requires continuous, active review of research requires that an IRB's workload be evenly distributed, with adequate resources for the IRB to engage in effective monitoring. Time represents the IRB's most critical resource. IRB members often face an overwhelming task, where some IRBs at large institutions monitor more than one thousand clinical trials at a time. Without a reduction in its workload, an IRB simply cannot spend enough time effectively monitoring clinical trials. In fact, a 1996 General Accounting Office study found that many IRBs often spend only one to two minutes of review per study.[213] Reducing an IRB's workload may include appointing more than one IRB to larger institutions, or possibly delegating tasks to smaller committees composed of IRB members.

4. Institutions Should Establish a Conflict of Interest Committee

As suggested by the Draft Interim Guidance, institutions should establish Conflict of Interest Committees, whose sole responsibility is to review the institution's and the investigator's conflicts of interest, particularly financial conflicts, and submit a report and recommendation to the IRB. A Conflict of Interest Committee should establish uniform criteria to apply to all conflicts, taking into consideration the role that the investigator with the conflict plays in implementing the protocol, ensuring that an independent investigator is in a position to oversee and manage investigators with financial conflicts, requiring annual audits of protocols to review financial conflicts, and ensuring that the institution implements policies and procedures to eliminate any danger that its financial conflicts may present to patients.

The IRB's role in evaluating the Conflict of Interest Committee's report and recommendation should include a determination of the frequency of review during the research and a determination of what, if any, financial conflict information merits disclosure in the patient consent form.

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213. GEN. ACCT. OFF., SCIENTIFIC RESEARCH: CONTINUED VIGILANCE CRITICAL IN PROTECTING HUMAN SUBJECTS (1996), *at* http://www.gao.gov (on file with the Notre Dame Journal of Law, Ethics & Public Policy).

B. *Establish One Agency to Oversee All Clinical Research*

While IRBs provide the first line of defense against unethical research, a government agency that is charged with overseeing research in general, and promulgating rules regarding research in particular, can provide a set of standards for IRBs, institutions, and research teams to follow in designing and implementing studies. Currently, that task falls to the OHRP. The OHRP, however, only oversees research that falls under HHS regulations. Additionally, the FDA only monitors research that falls under FDA guidelines. Creating one agency, however, could ensure effective and efficient oversight, with the ability to adapt to the changing research environment and changes in technology. Rather than complying with the laws of multiple government agencies, institutions, investigators, and IRBs could look to the single government agency and its uniform standards.

In establishing one agency to oversee clinical research, the agency should be granted the authority to oversee *all* medical research, thus providing safeguards for all patients in all studies. While current laws apply only to federally funded research or research involving drugs or treatments that must submit to FDA approval, oversight of all clinical research will ensure that *all* patients receive equal protection.

VI. CONCLUSION

The OHRP's Draft Interim Guidance and institutional policy changes like those recommended by The Hutch's Patient Protection Committee present varied responses to the problems presented by financial conflicts of interest in human subject research. While financial conflicts of interest are a relatively new issue in human subject research, conflicts of interest have always existed for investigators. From the promise of prestige to the pursuit of knowledge, medical researchers have always had a stake in the outcome of human subject research and, while financial interests represent a significant incentive in certain outcomes, medical researchers generally preferred one outcome over another even before they encountered financial interests.

The changes in medical research funding, leading to more private than public funding, the surge of biotechnology stock in the 1980s, and the move toward for-profit health care, led to increasing occurrences of financial agreements in medical research. On the other hand, the increase in private funding, in addition to the wealth created by biotechnology stock, resulted in an increase in medical research, benefiting both individual patients, future patients, and society. Eliminating financial con-

flicts of interest could potentially drastically reduce the amount of medical research and slow the movement to the discovery of cures or more effective treatments for numerous medical conditions. Financial incentives, therefore, play an important role in medical research; eliminating them may devastate the research community.

While financial conflicts of interest should not be eliminated altogether, they can be minimized and managed. Institutional Review Boards are in the best position to manage these conflicts. IRBs should strive to exercise independent judgment in determining whether to approve a research protocol, what to disclose in the patient's consent form, and how to manage financial conflicts of interest.

The IRB should determine whether to disclose financial conflict information in the patient consent form based, in addition to the issues posed by the Draft Interim Guidance,[214] on both the potential benefits to the patient (in other words, the underlying reason behind the patient's decision to consider participating in the protocol), and the alternative therapies that are available to the patient. A terminally ill patient, for instance, may consider participation because it represents the only potential cure, while a healthy volunteer may choose to participate for the benefit of society. In the middle of this spectrum is the patient who may choose to participate in the protocol, even though alternative proven therapies are available. While a terminally ill patient with no other alternatives may place little importance on financial incentives the investigator may have, a healthy volunteer or a patient with alternative treatment choices may take those conflicts into consideration when determining whether to participate in the protocol.

The IRB's role is to protect each of these patients. The healthy volunteer and the patient with alternative treatment choices can be protected by adequate disclosures of conflicts and disclosures of the institution's and the IRB's policies and procedures to manage those conflicts. The IRB can protect the terminally ill patient from an investigator's financial conflicts by ensuring that adequate safeguards are put into place, thus monitoring the protocol and, should the financial interests cloud the investigator's judgment, assuring that the patient is adequately represented in obtaining a remedy and determining the next course of treatment, including whether to continue the protocol under a new investigator or to terminate the protocol. One potential pitfall of requiring a patient consent form to disclose *all*

214. *See supra* note 187.

financial conflicts, rather than only those that an IRB determines merit disclosure, is a long, confusing patient consent form, cluttered with disclosures regarding insignificant conflicts of interest.

While informed consent does not, by itself, make research ethical, it is one safeguard that an IRB can implement to ensure patient protection. In addition, institutions and researchers should strive to not only create a culture of compliance, but a demonstrated commitment to patient protection, where patient protection is a principal factor in determining the next course of action, rather than another hurdle to overcome in implementing the next course of action. Such safeguards, implemented after considering the ethical principals identified in the Belmont Report, along with continuous, interactive monitoring of the clinical trials, allows an IRB, institution, and its research teams to focus on protecting patients, while developing beneficial treatments and medicine. Each institution, community, patient, and protocol is unique, and that uniqueness should be factored into each disclosure decision. While financial conflicts may never be fully eliminated, institutions and their IRBs can ensure that those conflicts do not damage the patient's integrity and autonomy. Using patients for profit is never acceptable, and IRBs, institutions, and clinical investigators should implement those policies and procedures that ensure that each patient is protected from overzealous decisions that result from a financial conflict. Even when a government agency does issue clear guidelines to manage financial conflicts, institutions and IRBs should continually review and, if necessary, revise their policies and procedures to reflect changes in research funding, the research community, and the changing needs of patients.