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## **TRUSTING DOCTORS: TRICKY BUSINESS WHEN IT COMES TO CLINICAL RESEARCH**

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## **TRUST IN THE M. D.-PATIENT CONTEXT**

**Fran Miller**

**Trust has been a thorny issue for medicine ever since the first patient made himself vulnerable in the hands of the first physician. Patients have had little choice but to trust their doctors when they must lay themselves bare, both physically and emotionally, for therapy to proceed on the basis of accurate information. The imbalance of power this creates is tolerable for patients only when they can trust their doctors. Historically, some doctors have lied to patients for “therapeutic reasons,” and others have lied to patients in the clinician’s own self interest. When these lies surface, the therapeutic relationship is almost always undermined.**

**Two twenty-first century trends, each coming from a different direction, are putting new pressure on trust between doctors and patients. The first emanates from rapidly accelerating use of the internet to equalize the information imbalance between patients and physicians. Patients are now able not only to understand, but to second-guess their doctors’ treatment recommendations in ways never before possible. The growing commercialization of medical practice, on the other hand, is generating financial conflicts of interest between the parties that threaten to undermine trust in the therapeutic relationship altogether. This session will explore these trends.**

# TRUSTING DOCTORS: TRICKY BUSINESS WHEN IT COMES TO CLINICAL RESEARCH

Frances H. Miller\*

“Medicine is, at its center, a moral enterprise grounded in a covenant of trust.

This covenant obliges physicians . . . to use their competence in the patient’s best interests.”<sup>1</sup>

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## I. Introduction

Twenty-first century currents threaten the traditional foundation of trust on both sides of the physician-patient relationship. Doctors and patients approach one another increasingly warily these days because each side has internalized an earful of negative stereotypes about the other. Many patients suspect that self-interested physicians will either deny them care because they earn more money by doing less for their patients,<sup>2</sup> or

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<sup>1</sup> Ralph Cranshaw et al., *Patient-Physician Covenant*, 273 JAMA 1553, 1553 (1995) (noting the various ethical dilemmas that currently challenge physicians).

<sup>2</sup> See Stephen M. Shortell et al., *Physicians as Double Agents: Maintaining Trust in an Era of Multiple Accountabilities*, 280 JAMA 1102, 1102 (1998) (discussing a study focusing on the pressures created by managed care). “[M]anaged care’s financial incentives for providers to skimp on care make it difficult for patients to trust that an advised course of action is in a patient’s true best interests.” Katherine Swartz, *The Death of Managed Care as We Know It*, 24 J. HEALTH POL. POL’Y & LAW 1201, 1205 (1999) (exploring whether the loss of patient trust will severely affect managed health care).

will persuade them to undergo unnecessary - even sometimes dangerous - therapy.<sup>3</sup>

Many doctors, on the other hand, fear that aggressive internet-savvy patients will second-guess treatment recommendations with imperfect knowledge, and sue the moment anything goes wrong.<sup>4</sup> All this is a far cry from the Norman Rockwell stereotype of the kindly old family physician and his grateful patients of fifty years ago.

This article will examine the troublesome ethical dilemmas arising out of physician conflicts of interest in the context of research on human beings.<sup>5</sup> The article will focus particularly on conflicts that permeate clinical trials of new drugs and devices.<sup>6</sup> It eschews discussion, however, of provider financial conflicts of interest associated with reimbursement methodologies,<sup>7</sup> provider scams, and other forms of financial exploitation

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<sup>3</sup> Cf. E. Haavi Morreim, *Conflicts of Interest for Physician Entrepreneurs*, in CONFLICTS OF INTEREST IN CLINICAL PRACTICE AND RESEARCH, 251 (Roy Spece et al. eds, 1996) (highlighting the ethical issues that arise when physicians refer patients to facilities in which they have a financial share).

<sup>4</sup> See Frances H. Miller, *Health Care Information Technology and Informed Consent: Computers and the Doctor-Patient Relationship*, 31 IND. L. REV. 1019, 1019 (1998) (examining the effects of the internet and other health care information technology on doctors and patients); *Web users Search for Medical Advice Most Often*, WALL ST. J., Nov. 27, 2000, at B14 (declaring medical information to be the most sought-after information on the internet).

<sup>5</sup> See generally Jerome P. Kassirer, *Medicine at Center Stage*, 328 NEW ENG. J. MED. 1268 (1993) (acknowledging that individual doctors' and researchers' actions have a tendency to undermine public confidence in the entire medical profession); Arnold S. Relman, *Economic Incentives in Clinical Investigations*, 320 NEW ENG. J. MED. 933, 933 (1989) (discussing the effects of commercialization on clinical research).

<sup>6</sup> Clinical trials are typically composed of three phases. Phase One trials test for safety of a new drug by measuring the side effects of increased doses. The results of these studies are used in the design of Phase Two trials for clinical efficacy. See 21 C.F.R. § 312.21(a)(1) (2000). Phase Two trials determine a drug's effectiveness for particular indications, and identify common side effects and risks of the drug. See §312.21(b). Phase Three trials further evaluate the safety and effectiveness, and the overall risk/benefit relationship, of a new drug in larger-scale clinical investigations. See § 312.21(c).

<sup>7</sup> See generally David Orentlicher, *Paying Physicians More to Do Less: Financial Incentives to Limit Care*, 30 U. RICH. L. REV. 155 (1996) (arguing that the financial incentives given to physicians to limit care will be both beneficial and effective); Marc A.

associated with payment for medical services.<sup>8</sup> Other articles have explored these trust-impairing trends in greater depth than this symposium's page limitations permit.

Today, the boundaries separating medical research from clinical practice are becoming increasingly hard to trace.<sup>9</sup> The problems associated with medical research manifest themselves in various areas of medical practice. For example, some drug and device manufacturers now compensate primary care physicians for enrolling their patients in clinical studies.<sup>10</sup> Often, these studies may be of little benefit or could possibly harm the subjects of these investigations. Another illustration involves surgeons who devise allegedly "better ways" to perform surgical procedures, such as making their initial incisions in a different area of the patient's torso from that generally used. These

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Rodwin, *The Organized Medical Profession's Response to Financial Conflicts of Interest: 1890-1992*, 70 MILBANK Q. 703 (1992) (presenting a historical analysis of physicians' financial conflicts of interest).

<sup>8</sup> Such manipulations associated with federally-reimbursed health services eventually led Congress to pass every provider's regulatory nightmare (and every lawyer's billable-hours dream): the federal fraud and abuse laws. *See generally* TIMOTHY JOST & SHARON DAVIES, *MEDICARE AND MEDICAID FRAUD AND ABUSE* (1998). *Cf.* James F. Blumstein, *The Fraud and Abuse Statute in an Evolving Health Care Marketplace: Life in the Health Care Speakeasy*, 22 AM. J.L. & MED. 205 (discussing the various attributes and spotty enforcement of the fraud and abuse statutes).

<sup>9</sup> *See* Dale H. Cowan and Eva Bertsch, *Innovative Therapy: The Responsibility of Hospitals*, 5 J. LEGAL MED. 219, 222-25 (1984). *Cf.* Marcia Angell, *Is Academic Medicine for Sale?*, 342 NEW ENG. J. MED. 1516, 1516 (2000) (noting the blurring of boundaries between academic medicine and industry).

<sup>10</sup> *See* Sheryl Gay Stolberg, *Biomedicine is Receiving New Scrutiny as Scientists Become Entrepreneurs*, N.Y. TIMES, Feb. 20, 2000, at 26 (highlighting the ethical problems associated with academic scientists becoming industrial entrepreneurs). *See generally* OFFICE OF INSPECTOR GENERAL, DEPARTMENT OF HEALTH AND HUMAN SERVICES, *RECRUITING HUMAN SUBJECTS: PRESSURES IN INDUSTRY-SPONSORED CLINICAL RESEARCH* (2000) (summarizing the Department of Health and Human Services' oversight of sponsor and investigator efforts to recruit human subjects for industry-sponsored clinical trials). According to the Department of Health and Human Services, an average of 4,237 human subjects were used in individual New Drug Applications between 1994 and 1995. *See id.* at 12. A New Drug Application is the initial culmination of the FDA approval process, permitting a new drug to be shipped in interstate commerce. *See id.*

surgeons have regulatory incentives to characterize their innovations as “quality improvements” rather than as experimental procedures. Doctors seeking to *experiment* on human beings must generally submit their research proposals to Institutional Review Boards (“IRBs”) for approval, because federal law charges these bodies with protecting the human subjects of clinical research.<sup>11</sup> IRB responsibilities include evaluating whether pre-clinical studies demonstrate the innovation's potential for reasonable safety and efficacy in human beings, and ensuring that the subjects of the research give their informed consent. This process entails red tape, delay, and often requires modification of the planned innovation.

This article focuses on the inevitable conflict between the objectives of clinical investigators and those of their human subjects to illuminate subtle divergences of interest in doctor-patient relationships that patients often do not recognize - or want to believe. Once perceived, however, these potentially corroding conflicts can stun research subjects and their families, and leave them feeling deeply betrayed by their clinicians.<sup>12</sup> Emotions of betrayal, in turn, have a tendency to spawn lawsuits.<sup>13</sup>

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<sup>11</sup> See 45 C.F.R. § 46 (1999); Federal Policy for the Protection of Human Subjects, 56 Fed. Reg. 117, 28003-28032 (1991) (describing federal policies implemented for the protection of human research subjects).

<sup>12</sup> Cf. *Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479 (Cal. 1990) (finding a breach of disclosure obligations where physicians established and patented a cell line from a patient’s T-lymphocytes without informing him that his tissue samples were being withdrawn for research with commercial potential).

<sup>13</sup> See generally Gerald B. Hickson, et al., *Factors that Prompted Families to File Medical Malpractice Claims Following Perinatal Injuries*, 267 JAMA 1359 (1992) (identifying self-reported reasons that prompt families to file malpractice claims following perinatal injuries); Marilyn Vincent et al., *Who Sues Their Doctors? How Patients Handle Medical Grievances*, 24 L. & SOC’Y REV. 105 (1990) (examining the dispute resolution choices that dissatisfied patients made in response to unsatisfactory medical experiences).

In a 1999 lawsuit, the family of eighteen-year-old Jesse Gelsinger, a participant in a Phase One safety trial<sup>14</sup> of a gene-transfer procedure, charged the University of Pennsylvania with Jesse's wrongful death. The plaintiffs alleged, among other things, that the investigators had failed to disclose their financial ties to the company whose experimental product was being tested for safety.<sup>15</sup> Dr. James Wilson, the director of the university's Institute for Gene Therapy, held an ownership interest in the company whose product was being evaluated in the trial which he later sold for \$13.5 million.<sup>16</sup> The University settled the case for an undisclosed - but substantial - sum within a matter of weeks.<sup>17</sup>

In addition to discussing the problems of conflicts of interest in clinical trials, this article notes patients' steadily growing use of the internet to evaluate their physicians and hospitals, to question provider recommendations for therapy, to gain access to clinical trials, and even to secure treatment. This increasing tendency for patients to obtain medical information from the internet, combined with conflicts of interest between researchers and human subjects, has the potential to destroy the delicate therapeutic interplay on both sides of the physician-patient relationship. If these potentially destabilizing trends are managed creatively, however, they could improve both the physician-patient relationship and the overall quality of care.<sup>18</sup>

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<sup>14</sup> See *supra* note 6 (discussing the characteristics of Phase One trials).

<sup>15</sup> See *Family Sues University Over Gene Therapy Death*, BOSTON GLOBE, Sept. 20, 2000, at A24 (reporting on the Gelsinger lawsuit and its impact on other gene therapy programs).

<sup>16</sup> See *Penn, Gene Therapy Doctors Settle Suit in Death of Teen*, PATRIOT-NEWS HARRISBURG, November 5, 2000, at A9.

<sup>17</sup> See *Huntly Collins, Penn, Family Settle Suit in Gene Therapy Death*, PHILADELPHIA INQUIRER, November 4, 2000, at A1.

<sup>18</sup> See, e.g., Donald W. Moran, *Health Information Policy: On Preparing for the Next War*, 17 HEALTH AFF. 9 (1998) (discussing the need for conscious health information

## II. Background

Trust has always been deemed a critical component of the therapeutic relationship.<sup>19</sup> Traditional healing theory is based on the idea that patients must trust their care-givers enough to lay themselves bare, both physically and emotionally, so the true causes of illness can be understood.<sup>20</sup> Most analysts consider patients' trust in their physicians integral to healing itself,<sup>21</sup> in part because of the well-documented placebo effect. Approximately one-third of all patients respond positively to placebo therapy, including placebo surgery, in some positive way, regardless of the underlying medical problem.<sup>22</sup> This phenomenon presumably occurs because patients believe that the therapy their doctors endorse for them will help.<sup>23</sup> In other words, for many patients, trust in their doctors is an essential element of the healing process.

Medical ethics and the law have sought to counter the imbalance of power- often intensified by information inequalities- in the doctor-patient relationship. The law

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policy); Liz Kowalczyk, *Online Medical Records Seen Empowering Patients*, BOSTON GLOBE, July 31, 2000, at A1 (surveying one internet medical source and its effects on patients and physicians).

<sup>19</sup> See generally JAY KATZ, *THE SILENT WORLD OF DOCTOR AND PATIENT* (1984) (exploring the effects of trust and communication on the physician-patient relationship).

<sup>20</sup> See generally Ezekial J. Emanuel & Nancy N. Dubler, *Preserving the Physician-Patient Relationship in the Era of Managed Care*, 273 JAMA 323 (1995) (discussing how choice, competence, communication, compassion, continuity, and "no conflict" constitute the ideal physician-patient trust relationship).

<sup>21</sup> For one reason, patients who trust their doctors are more likely to comply with their medical advice.

<sup>22</sup> See Alan G. Johnson, *Surgery as a Placebo*, 344 THE LANCET 1140, 1141 (1994) (claiming that the placebo effect must be taken into account in order to make an objective assessment of the outcome of surgery); cf. Ruth Macklin, *The Ethical Problems with Sham Surgery in Clinical Research*, 341 NEW ENG. J. MED., 448 (1999) (warning that some placebo controls in surgical trials may be unethical).

imposes fiducial-type<sup>24</sup> duties on the physician as a means of restoring the balance.<sup>25</sup>

Fiducial obligations also address the doctor's powerful role in determining therapeutic choices. The uncertainties inherently associated with medicine,<sup>26</sup> although not commonly appreciated by laypeople, mean that judgment calls permeate many therapeutic decisions.<sup>27</sup>

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<sup>23</sup> See K.B. Thomas, *The Placebo in General Practice*, 344 THE LANCET 1066, 1067 (1994) (concluding that overall the placebo effect is harmful to medicine); R. Houston, *The Doctor Himself as Therapeutic Agent*, 11 ANNALS INT. MED. 1415 (1938).

<sup>24</sup> I deliberately eschewed stating that the law imposes *fiduciary* duties on physicians, notwithstanding the fact that judges and commentators often use fiduciary terminology, because fiduciary terminology is generally used to describe relationships of trust with respect to property, not persons. See Sarah Worthington, *Fiduciaries: When Is Self-Denial Obligatory?*, 58 CAMBRIDGE L.J. 500, 507-08 (1999) (discussing the dangers of classifying all fiduciary relationships under the same uniform law). The obligations the law imposes on doctors can be both broader and narrower than the sphere generally applicable to other fiduciaries. See RESTATEMENT (SECOND) OF TRUSTS § 2 cmt. b (1959) (characterizing doctor-patient transactions as “confidential relations” rather than “fiduciary relations”); Council on Ethical and Judicial Affairs, American Medical Association, *Conflict of Interest: Physician Ownership of Medical Facilities*, 267 JAMA 2366, 2367 (1992) (recommending that physicians should not refer patients to a health care facility at which they did not directly provide care when they have an investment interest in the facility); Marc A. Rodwin, *Strains in the Fiduciary Metaphor: Divided Physician Loyalties and Obligations in a Changing Health Care System*, 21 AM. J.L. & MED. 241, 242 (1995) (noting the broadening and narrowing of doctors' fiduciary obligations, especially in light of the fact that today's health care policy focuses on groups rather than individuals).

<sup>25</sup> See *Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479, 483 (Cal. 1990) (“a physician's failure to disclose . . . [personal] interests may give rise to a cause of action for . . . breach of fiduciary duty.”); *Neade v. Portes*, 710 N.E.2d 418, 427 (Ill.App. 2d 1999) (holding that a plaintiff may plead breach of fiduciary duty against physician, apart from negligence claim). See, e.g., *Canterbury v. Spence*, 464 F.2d 772, 783-85 (D.C. Cir. 1972) (using such phrases as “duty to disclose” and “conduct reasonable under the circumstances” to describe the legal standards applicable to doctors).

<sup>26</sup> See JEROME GROOPMAN, *SECOND OPINIONS* (2000) (demonstrating the prevalence of scientific doubt through an account of a patient with a life-threatening bone marrow ailment whom the author wanted to treat in a manner opposed to that advocated by the patient's New York doctor. The author and his counterpart engaged in a struggle for their patient's trust, neither one of them at all sure whether he was right.).

<sup>27</sup> George Bernard Shaw put it succinctly in his introduction to *THE DOCTOR'S DILEMMA*, “I presume nobody will question the existence of a widespread popular delusion that every doctor is a man of science . . . . As a matter of fact, the rank and file

Physicians are expected to put their patients' interests ahead of their own when exercising clinical judgment, and the common law spins out this fiducial-type duty in many ways. For example, the law does not permit doctors to abandon their patients once therapy has begun, regardless of whether they have been paid, because patients have a reliance interest in continuing treatment.<sup>28</sup> Similarly, the law requires clinicians to keep all personal information they obtain about their patients during the course of therapy confidential. This obligation promotes candor on the patient's part, and enables therapy to proceed on the basis of presumably accurate facts.<sup>29</sup> Furthermore, over the past half-century both statutes<sup>30</sup> and common law<sup>31</sup> have imposed an increasingly expansive duty of disclosure on physicians. The policy rationale holds that better information enables patients to exercise more autonomy when they evaluate physician-recommended

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of doctor are no more scientific than their tailors; or, if you prefer to put it the reverse way, their tailors are no less scientific than they.” GEORGE BERNARD SHAW, *THE DOCTOR’S DILEMMA* 19-20 (1932) (exploring society’s perceptions of a doctor’s duties).

<sup>28</sup> See *Hammonds v. Aetna Cas. & Sur. Co.*, 243 F. Supp. 793, 805 (N.D. Ohio 1965) (holding that a doctor may discontinue treatment only after his patient has been afforded reasonable notice and has had opportunity to secure other medical attention); *Ricks v. Budge*, 64 P.2d 208, 211 (Utah 1937) (ruling that a physician must continue his service so long as attention is required).

<sup>29</sup> The physician’s duty to maintain patient confidentiality stems from the Hippocratic Oath, which reads: “Whatever, in connection with my professional practice . . . I see or hear in the life of men which ought not to be spoken abroad I will not divulge as recommending that all such should be kept secret.” HIPPOCRATES, *GREAT BOOKS OF THE WESTERN WORLD, HIPPOCRATIC WRITINGS* (Roberty Maynard Hutchins ed. & Francis Adams trans., Encyclopedia Britannica, Inc. 1952); see also *AMERICAN MEDICAL ASSOCIATION PRINCIPLES OF MEDICAL ETHICS, DUTY OF CONFIDENTIALITY, CURRENT OPINIONS OF THE JUDICIAL COUNCIL OF THE AMERICAN MEDICAL ASSOCIATION* (1984) (spelling out the duty of confidentiality). *But see Tarasoff v. Regents of Univ. of Cal.* 551 P.2d 334, 342 (Cal. 1976) (limiting the duty of confidentiality when a psychiatrist becomes aware that the patient presents a threat of danger to society).

<sup>30</sup> See, e.g., MASS. GEN. LAWS ANN. ch. 111, § 70E (West 2000) (guaranteeing patients the right to inspect medical records and receive other information concerning financial assistance or treatment).

treatment.<sup>32</sup> Other examples of doctors' heightened duty to patients abound, but these paint the general picture with regard to fiducial-type obligations.

All this seemed to work fairly well to maintain a reasonable balance of trust in doctor-patient relationships until the last couple of decades. As health care has increasingly embraced the market model, however, potential conflicts of interest between physician and patient have assumed greater visibility.<sup>33</sup> Moreover, as new technology and pharmaceuticals have brought doctors expanded scope for simultaneously treating patients and making money, many physicians have discovered creative ways to align their self-interest, financial and otherwise, with patient therapy.<sup>34</sup> Although some doctors

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<sup>31</sup> See, e.g., *Johnson v. Kokemoor*, 545 N.W.2d 495, 498 (Wis. 1996) (holding that patients may not make informed decisions about their treatment unless the physician discloses viable alternatives to and risks of the treatment proposed).

<sup>32</sup> See *Cobbs v. Grant*, 502 P.2d 1, 10 (Cal. 1972) (noting that reasonable knowledge of treatment alternatives is essential to an informed decision); *Bernard v. Char*, 903 P.2d 676, 683 (Haw. App. 1995) (discussing the informed consent doctrine); T.L. BEAUCHAMP AND J. CHILDRESS, *THE PRINCIPLES OF BIOMEDICAL ETHICS*, c. 3 (2001); Mary Anne Bobinski, *Autonomy and Privacy: Protecting Patients from Their Physicians*, 55 U. PITT. L. REV. 291, 330 (1994) (discussing how a duty to disclose maximizes the autonomy of both providers and patients).

<sup>33</sup> See generally MARC RODWIN, *MEDICINE, MONEY AND MORALS* (1993); Morreim, *supra* note 3, at 251 (highlighting the ethical issues that arise when physicians refer patients to facilities in which they are investors); Arnold S. Relman, *The New Medical-Industrial Complex*, 303 NEW ENG. J. MED. 963 (1980) (noting the recent rise of health-care services for profit); Arnold S. Relman, *Medicine as a Profession and a Business*, in *THE TANNER LECTURES ON HUMAN VALUES*, 283 (Sterling M. McMurrin, ed., 1988) (explaining how traditional medical ethics are currently challenged by new social, economic, and political realities).

<sup>34</sup> See Theodore N. McDowell, Jr., *Physician Self Referral Arrangements: Legitimate Business or Unethical 'Entrepreneurialism,'* 15 AM. J.L. & MED. 61, 61-64 (1989) (analyzing the policy debate surrounding physician self-referral arrangements); Dennis F. Thompson, *Understanding Financial Conflicts of Interest*, 329 NEW ENG. J. MED. 573, 573 (1993) (identifying a rise in conflicts of interest involving physicians, in the areas of self-referral, sharing in HMOs and hospitals, gifts from drug companies and other areas).

view this development as a win-win situation,<sup>35</sup> many patients, the common law, and increasingly the government are skeptical.

While the market was transforming medicine into a more entrepreneurial mode in the 1980s and 1990s, technology was ameliorating the traditional information imbalance between doctors and their patients.<sup>36</sup> The widespread use of computers and the internet have enabled laypeople to gain access to medical and provider information that was considered inaccessible and beyond their understanding a mere decade ago. According to a recent poll, ninety-eight million Americans currently turn to the internet for health information, up from half that number two years ago.<sup>37</sup> Today, individuals can not only obtain relevant scientific information quickly and easily through patient-friendly websites<sup>38</sup> and resource centers,<sup>39</sup> but the growing availability of physician, hospital, and managed care plan profiles and scorecards makes it easier to compare providers and insurers with their competitors.<sup>40</sup> Some websites allow patients to compare the clinical

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<sup>35</sup> See CONFLICTS OF INTEREST IN CLINICAL PRACTICE AND RESEARCH, *supra* note 3, at x (“Because physicians are not trained to look for conflicts of interest, they often find themselves enmeshed in them without recognizing the problem.”).

<sup>36</sup> See generally Miller, *supra* note 4, at 1023 (examining the effects of the internet and other health care information technology on doctors and patients).

<sup>37</sup> See Janlori Goldman, Zoe Hudson, *Virtually Exposed: Privacy & E-Health*, 19 HEALTH AFF. 6 (2000) (discussing the privacy issues related to health-related internet websites).

<sup>38</sup> See Tara Parker-Pope, *Six Steps to Help You Start Your Own Search for Medical Answers*, WALL ST. J., August 11, 2000, at B1 (suggesting medical information-gathering methods via the internet); <<http://www.oncolink.org>> (referencing up-to-date cancer information for internet users).

<sup>39</sup> See Miller, *supra* note 4, at 1037 n.108 (describing hospital-based patient information centers).

<sup>40</sup> See, e.g., <<http://www.docboard.org>> (providing physician profiles in selected states including Massachusetts); <<http://www.ncqa.org>> (providing evaluations of managed care plans).

outcomes of specific doctors and hospitals.<sup>41</sup> Moreover, patients today can easily obtain second-opinions via the internet, and in some instances, even secure prescriptions<sup>42</sup> and receive treatment<sup>43</sup> for their self-reported ailments.

Finally, high-profile events such as the Institute of Medicine's 1999 study of error in medicine have raised patient consciousness about the dangers inherent in all doctor-patient encounters.<sup>44</sup> The study's widely reported page-one statement remarks that "deaths due to medical errors exceed the number attributable to the eighth leading cause of death."<sup>45</sup> The net result is that these web-enhanced "advances" shake the general level

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<sup>41</sup> See Edward Hannan, et al., *Improving the Outcomes of Coronary Artery Bypass Surgery in New York State*, 271 JAMA 761, 761 (1994) (concluding that the collection and dissemination of risk-adjusted mortality data for CABG surgery played a significant role in the observed declining death rate).

<sup>42</sup> See Katrina Armstrong, *Direct Sale of Sildenafil (Viagra) to Consumers Over the Internet*, 341 NEW ENG. J. MED. 1389, 1389 (1999) (reviewing 77 websites selling Viagra, of which 31 did not require answers to a health questionnaire before delivering the drug); see also Douglas Carnall, *Website of the Week: Viagra*, 318 BRIT. MED. J. 338 (1999) (highlighting briefly the various internet sources related to Viagra); Cathy Perlmutter, *What You Should Know About Prescribing on the Web*, 14 HIPPOCRATES 39 (2000) (warning patients to be wary of many internet prescribing sites); <<http://www.kwikmed.com/viagra/1012297/is>> (advertising Viagra without a prescription for six dollars per dose); <<http://www.viapro.com>> (providing Viagra via the internet).

<sup>43</sup> See Brian Darer, *Telemedicine: A State-Based Answer to Health Care in America*, 3 VA. J.L. & TECH. 4, 4 (1998) (discussing the effects of "telemedicine," health care consultation and education using telecommunications networks.); Patricia C. Kuszler, *Telemedicine and Integrated Health Care Delivery: Compounding Malpractice Liability*, 25 AM. J.L. & MED. 297, 297 (1999) (asserting that access, quality, and cost of health care may all improve, but traditional norms may change).

<sup>44</sup> See Atul Gawande, *When Doctors Make Mistakes*, NEW YORKER, Feb. 1, 1999, at 40 (exploring the inevitability of medical mistake, and the need to keep aiming for perfection).

<sup>45</sup> See TO ERR IS HUMAN: BUILDING A SAFER HEALTH SYSTEM 1 (Linda T. Kohn et al. eds., 1999) (reporting on the quality of health care in America).

of trust between physicians and their patients. Such reduced levels of trust can generate defensive counter-measures that interfere with the goals of therapy.<sup>46</sup>

### III. *Conflicts of Interest in Clinical Research*

Discussing conflicts of interest in clinical research with doctors and patients in the abstract is seldom productive. At an intellectual level, most physicians and many patients understand that clinical researchers have objectives- including professional recognition and advancement- that could conflict with some of their patients' best medical interests. Such conflicts may persist regardless of whether the researcher has a direct financial interest in the outcome of the particular study. Many doctors bridle at the notion, however, that clinical researchers are easily tempted to be "unethical" when their self-interest is directly involved. Often they resist precautionary measures that they believe unfairly taint the whole profession for the misdeeds of a few.<sup>47</sup>

Research physicians realize that success depends upon their ability to produce reliable scientific results which can be published or otherwise used to obtain professional advancement. Reliable scientific results are also the key to FDA approval, federal

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<sup>46</sup> See Robert T. Golembiewski and Mark McKonkie, *The Centrality of Interpersonal Trust in Group Processes*, in THEORIES OF GROUP PROCESSES (Cary L. Cooper and Eric Miller, Eds. 1975).

<sup>47</sup> See Kenneth J. Rothman, *Conflict of Interest: The New McCarthyism in Science*, 269 JAMA 2782, 2782-84 (1993) (arguing that mandatory disclosure of an author's possible conflict of interest is unnecessary during the editorial review stage and may impair an editors' ability to judge scientific work solely on its merits); Kenneth J. Rothman, *The Ethics of Research Sponsorship*, 44 J. CLIN. EPIDEMIOLOGY 25S, 25S-28S (1991) (arguing that mandatory identification of funding sources and prohibition of financial connection between an investigator and a company whose product is studied will impair merit-based evaluation and promote *ad hominem* evaluation).

research dollars, and future funding from drug and device manufacturers.<sup>48</sup> These researchers also know that in order to produce useful results they will need human subjects for their studies, in addition to their animal counterparts.<sup>49</sup> Although physicians may have read or been told that human subjects gain little or no health benefit from participating in most experimental studies,<sup>50</sup> few give much credence to the notion.<sup>51</sup>

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<sup>48</sup> See Fergus Macbeth and Richard Stephens, *Marketing Clinical Trials*, 348 THE LANCET 111, 111 (1996) (discussing the various financial, academic, and professional rewards clinicians receive for their participation in clinical trials); see also Richard Delgado and Helen Leskovac, *Informed Consent in Human Experimentation: Bridging the Gap Between Ethical Thought and Current Practice*, 34 U.C.L.A. L. REV. 67, 104 (1986) (discussing the academic researcher's goals of grants, laboratory space, qualified graduate students, promotion, and tenure, all of which may lead to an under-valuation of informed consent); BERNARD BARBER, ET AL., RESEARCH ON HUMAN SUBJECTS: PROBLEMS OF SOCIAL CONTROL IN MEDICAL EXPERIMENTATION 59-92 (1973) (analyzing studies which suggest that the conflicting goals sought by scientific research and therapy may lead doctors in both the larger scientific community and the local institutional level to adopt overly permissive standards for humane treatment). Cf. Leonardo D. De Castro, *Exploitation in the Use of Human Subjects for Medical Experimentation: A Re-Examination of Basic Issues*, 9 BIOETHICS 259 (1995) (focusing on cultural and socio-economic differences that can impair patient understanding and consent).

<sup>49</sup> In 1995, an average of more than four thousand human subjects participated in clinical trials of each new drug that made it through the FDA process. See OFFICE OF THE INSPECTOR GENERAL, DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 10, at 12; see also R. Alta Charo, *Human Subjects Have It Worse Than Guinea Pigs*, 45 CHRON. HIGHER EDUC. 42, A64 (1999), (noting that oversight of the use of animals in scientific research is more thorough than oversight of the use of human subjects).

<sup>50</sup> For example, "objective therapeutic benefit has traditionally been described as being quite low, less than five %" in Phase One oncology trials. Christopher K. Daugherty et al., *Quantitative Analysis of Ethical Issues in Phase I Trials: A Survey Interview Study of 144 Advanced Cancer Patients*, 22 IRB 6, 11 (May-June 2000), (citing, *inter alia*, DD Van Hoff and J. Turner, *Response Rates, Duration of Response, and Dose Response Effect in Phase I Studies in Antineoplastics*," 9 INVESTIGATIONAL NEW DRUGS 1991, 115-22.).

<sup>51</sup> American pharmaceutical companies often defend their high drug prices by arguing that only one in every ten drugs successfully reaches the market. This low success rate is partially attributed to clinical investigators' inability to prove that the products are safe and effective enough for human consumption. See David Noonan, *Why Drugs Cost So Much*, NEWSWEEK, Sept. 25, 2000, at 26 (exploring the high cost of prescription medications in the context of the 2000 presidential election). Clinical trials are fundamentally comparative at the Phase Two and Phase Three (efficacy) stages, where two or more clinical interventions are compared for effectiveness. In the "gold standard"

Most seriously ill patients do not want to acknowledge that a clinical trial will probably not help their condition. Instead, these desperate souls want to believe in the omnipotence of medicine.<sup>52</sup>

When it comes to specific cases, most doctors and patients manage to convince themselves that the term “experimental therapy” is not an oxymoron.<sup>53</sup> An experimental study, by its definition, evaluates clinical interventions not yet scientifically proven to be of therapeutic benefit to patients. The whole purpose of a clinical experiment is to gather proof about the safety and efficacy of a proposed treatment. How, then, can researchers legitimately label an experimental drug or device as “therapy” while it is *being* evaluated, since clinical results have not yet confirmed its safety and efficacy? For this very reason, human participants in clinical trials are not usually referred to as patients, but rather as the “subjects” of research protocols.

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randomized controlled trial, one intervention is always a placebo. Although the subject may experience a positive placebo effect, this effect is usually only temporary, and is not attributed to the drug under study. See INSTITUTE OF MEDICINE, EXTENDING MEDICARE REIMBURSEMENT TO CLINICAL TRIALS 17-22 (2000).

<sup>52</sup> Most patients whose doctors conducted or suggested participating in clinical studies reason that “my doctor would not have asked me to do it if he did not think it would help me.” This reasoning persists even if the patient is aware that there is only a remote chance that participation will be beneficial. “The power of the [research subject’s] mind to hear only that which fits its preconception [that participating in an experimental trial will benefit him] cannot be over-estimated. In addition, it is questionable whether investigators would be willing to be quite so brutal about sheltering subjects’ therapeutic misconceptions. The potential benefit, after all, is one of the most powerful incentives for subjects to agree to take part in research projects[.]” Paul Appelbaum, *The Therapeutic Misconception: Informed Consent in Psychiatric Research*, 5 INT. J. OF L. AND PSYCHIATRY 319, 328-29 (1982).

<sup>53</sup> See Nancy M.P. King, *Experimental Treatment: Oxymoron or Aspiration?* 25 HASTINGS CTR. REP. 6, 8 (1995) (noting that physicians and patients often urge insurance reimbursement for experimental treatment even when the likelihood of benefit is uncertain because they feel that technology assessment is too time consuming when faced with life-threatening illness); Jay Katz, *Human Experimentation and Human Rights*, 38 ST. LOUIS U. L.J. 7, 17 (1993) (discussing how both patients and doctors too eagerly dismiss the conflict between the interests of patients and the interests of science).

Powerful psychological forces enable clinical researchers to expose human subjects to risk in order to generate valid scientific results.<sup>54</sup> To justify this risk, physicians rationalize that even the most experimental of studies *might* help the human research subjects. Moreover, they often manage to convince themselves - as do most subjects of their experiments<sup>55</sup> - that any given participant is just as likely to end up in the beneficial category as any other.

The well-known Boston cardiologist Jeffrey Isner avers that he explains to patients all the risks involved with participating in his gene therapy experiments that are designed to grow new blood vessels bypassing blocked arteries in the heart or legs. Dr. Isner cautions subjects “not to consider the experiment as therapy,”<sup>56</sup> but then tells them that the experiment is like “a roll of the dice.”<sup>57</sup> Most subjects will overestimate their chances of “winning” when that particular metaphor is employed to describe the risk/benefit ratio of clinical trials. Rationally most patients would conclude that since each die has six sides (twelve when two are rolled), their doctor’s use of the gambling metaphor means that they have at least a one in twelve chance of “winning.” The whole

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<sup>54</sup> “He has an amazing ability to compartmentalize . . . [Jesse Gelsinger’s death] and remain objective . . . and emphasize what we can learn from it.” Comment of the University of Pittsburgh’s Chairman of the department of molecular genetics and biochemistry about Dr. James Wilson, director of the University of Pennsylvania’s Institute for Human Gene Therapy, and lead researcher on the gene therapy experiment that killed Gelsinger. See Collins, *supra* note 17, at A1. Dr. Wilson held an ownership interest in the company whose product was being evaluated in the trial, which he later sold for \$13.5 million. See Penn, *Gene Therapy Doctors Settle Suit in Death of Teen*, *supra* note 16.

<sup>55</sup> For example, a recent study found that ninety percent of patients with advanced cancer taking part in Phase One clinical trials think they will receive medical benefit from participating. See Daugherty, *supra* note 50, at 10.

<sup>56</sup> Alice Dembner and Liz Kowalczyk, *Doctor Stirs Questions on Genetics’ Frontier*, BOSTON GLOBE, May 21, 2000, at A1.

<sup>57</sup> Richard Saltus, *Doctor Rebuts FDA Citations: Lapse Tied to Gene Patient’s Death Report*, BOSTON GLOBE, May 19, 2000, at A1.

scientific objective of Dr. Isner's gene therapy studies, however, has been to discover whether patients have *any* chance of benefiting, let alone one in twelve. Therefore, Isner's use of the dice metaphor is deceptive.

Recently, Dr. Isner's questionable research practices generated public concern. He failed to report a patient death occurring two days after the gene transfer to Saint Elizabeth's Hospital, as required by federal regulations. In addition, he erroneously enrolled a cancer patient who should have been excluded from a trial. In the wake of these and other alleged violations, the FDA suspended Dr. Isner's gene therapy research in February 2000.<sup>58</sup> Since then, much of Dr. Isner's research has resumed.<sup>59</sup> The most troubling aspect of these events is that both Dr. Isner and Saint Elizabeth's Hospital hold substantial financial stakes in Vascular Genetics, a company which Isner co-founded and whose product was being evaluated in his studies. Although the hospital and Isner have stated that their ownership interests do not affect the conduct of the trials, their self-serving declarations do not instill confidence in the scientific objectivity of the results.

With hindsight, a research subject's health may indeed turn out to be significantly improved by participating in an experimental study. The chances of improvement, however, are statistically unlikely in most experimental protocols. In fact, many experimental subjects are randomized to the conventional therapy or placebo arm of the clinical trial and receive no innovative treatment at all.<sup>60</sup> To characterize Phase One and

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<sup>58</sup> See Dembner, *supra* note 56 ("Amid a national review of gene therapy experiments . . . Isner's experiments were halted in February.")

<sup>59</sup> See Anne Bernard, *Couple Donates \$1M to Gene Therapy Program*, BOSTON GLOBE, Jan. 26, 2001, at B1; Alice Dembner, *Boston Researcher to Resume Gene Study*, BOSTON GLOBE, November 14, 2000, at B14 (stating the hospital's intent to resume gene studies in which neither Dr. Isner nor the hospital held a financial interest);

<sup>60</sup> See *supra* note 50 (discussing the low objective therapeutic benefits of clinical trials).

Phase Two stages of clinical trials as “experimental therapy” is, at best, an exercise in mutual self-deception, and at worst, could constitute deliberate misrepresentation.

Recent litigation controversies over insurance reimbursement for the “compassionate use” of autologous bone marrow transplantation (ABMT) for metastatic breast cancer patients exemplify another concern about clinical research. These cases highlight the dangers of adopting experimental drugs and procedures for clinical use before researchers have compiled sufficient scientific evidence about their safety and efficacy.<sup>61</sup> When clinical use of a drug becomes widespread before experimental studies are concluded, researchers encounter difficulty enrolling additional patients in the randomized controlled trials of the drug - the gold standard for determining safety and efficacy. Few patients will chance randomization to the control group once they believe they believe, rightly or wrongly, that the drug is effective. In the case of ABMT, thousands of women suffered needlessly in the terminal stages of illness by choosing to undergo the grueling but essentially futile protocol. In addition, a significant percentage of them had their lives shortened because they were literally killed by the “experimental therapy.”

Nonetheless, drug and device manufacturers increasingly target their marketing efforts around large clinical studies, stimulating patient demand for access to “experimental therapy” before the full empirical evidence on safety and efficacy is in.<sup>62</sup>

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<sup>61</sup> See Gina Kolata and Kurt Eichenwald, *Business Thrives on Unproven Care, Leaving Science Behind*, N.Y. TIMES, October 3, 1999, at A1 (reporting on studies showing women with advanced breast cancer did just as well (i.e. poorly) when they had conventional chemotherapy as when they had the much more costly, risky, and quality-of-life impairing bone marrow transplantation procedure).

<sup>62</sup> See generally *Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research*, OFF. INSPECTOR GEN., DEP'T HEALTH AND HUM. SERVICES, 19, 20-21 (June 2000) (noting that because advertisements are expensive, they are cost-effective only for

Moreover, governments busily aid the drug manufacturers in this endeavor. The state of Maryland recently passed legislation mandating that all health insurers doing business in the state pay the clinical costs associated with subscriber enrollment in certain types of clinical trials.<sup>63</sup> In another troubling development, President Clinton issued an executive memorandum in 2000 directing the Health Care Financing Administration (HCFA) to cover Medicare patients' "routine medical costs of participation in a clinical trial."<sup>64</sup> When trusting senior citizens are encouraged to serve as laboratory animals for the rest of the population, our moral antennae ought to go up.

Putting aside the inflationary impact of these governmental decisions on total health care costs, both of these changes - which were strongly supported by the pharmaceutical industry - clearly encourage medically unsophisticated patients to seek access to "experimental therapy" before it has been deemed safe and effective. This should raise serious ethical concerns for us all.

In May of 2000, the Journal of the American Medical Association published an already widely read and widely quoted<sup>65</sup> essay entitled *What Makes Clinical Research Ethical?*<sup>66</sup> The article set forth seven basic requirements for ethical research, culled

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studies of common diseases, and further commenting that such advertisements and news stories blur the line between research and treatment, generating interest in clinical trials despite the lack of evidence of efficacy).

<sup>63</sup> See MD. CODE ANN., Insurance §15-827 (Supp. 2000) (mandating health insurance coverage for qualified clinical trials dealing with cancer or other life-threatening conditions).

<sup>64</sup> See Memorandum on Increasing Participation of Medicare Beneficiaries in Clinical Trials, 36 WEEKLY COMP. PRES. DOC. 1311, 1312 (June 7, 2000) (directing the Department of Health and Human Services to revise Medicare program guidance to authorize coverage of routine costs associated with clinical trials).

<sup>65</sup> See, e.g., *Risky Business: Improving the Protection of Patients in Clinical Research*, 8 BIOETHICS BULL. 1 (Spring/Summer 2000).

<sup>66</sup> Ezekiel J. Emanuel et al., *What Makes Clinical Research Ethical?*, 283 JAMA 2701 (2000).

from, *inter alia*, the Nuremberg Code,<sup>67</sup> the Declaration of Helsinki,<sup>68</sup> the Belmont Report,<sup>69</sup> and the International Ethical Guidelines for Biomedical Research Involving Human Subjects.<sup>70</sup> The essay summarized the human subject protection rationale underlying each of these consensus statements,<sup>71</sup> and cited an impressive and extended list of footnoted sources analyzing the ethical issues involved in experimental studies.<sup>72</sup>

The authors of the essay never allude to the fact that a clinical researcher's conflicts of interest, financial or otherwise, also pose serious impediments to the conduct of ethical research on human subjects. Instead, the article focuses on study value and design, a favorable risk-benefit ratio for the subject, independent review, and respect for subjects, including the right to give (and withhold) informed consent.<sup>73</sup> Although these are critically important issues, minimizing investigator conflicts of interest is equally crucial to long-term public support for experimental research and intensely important to the human subjects of those studies.

This complete failure to address conflicts of personal interest between clinical investigator and research subject in an article purporting to synthesize ethical research principles constitutes a startling omission in today's market-oriented medical arena.

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<sup>67</sup> The Nazi war crimes trials enunciated the Nuremberg Code as a set of ethical principles governing the conduct of research involving human experimentation. On the role of physicians in implementing Hitler's extermination policies, see R. J. Lifton, *THE NAZI DOCTORS* (1986).

<sup>68</sup> The Declaration of Helsinki, which elaborated on the Nuremberg Code, was adopted by the World Medical Association in 1964. See *Declaration of Helsinki*, in *THE NAZI DOCTORS AND THE NUREMBERG CODE* 331-36 (George Annas & Michael Godin Eds. 1992).

<sup>69</sup> *The Belmont Report*, NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH (1978).

<sup>70</sup> *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, WORLD HEALTH ORGANIZATION (1993).

<sup>71</sup> See Emanuel, *supra* note 66, Table 2, at 2703.

<sup>72</sup> See Emanuel, *supra* note 66, at 2710-11.

When a physician has a direct financial interest in the outcome of an experimental study (as when she receives consulting or patient referral fees from,<sup>74</sup> or has an ownership interest in, the firm producing the drug or device being evaluated<sup>75</sup>), her incentive to generate (preferably positive) results from experimental studies is undeniably strong.<sup>76</sup> Even if the researcher's interest is a personal one associated with professional advancement rather than financial compensation, the pressure to produce "meaningful results" can tragically undermine the human subject's health and well-being.

One need only be reminded of the Nazi doctors<sup>77</sup> or the Tuskegee syphilis studies<sup>78</sup> to bring home the point with a vengeance. Even the best-intentioned clinical investigators face temptation to skew study designs to insure that meaningful results will be forthcoming.<sup>79</sup> Those designs may (unwittingly or not) compromise patient

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<sup>73</sup> See Emanuel, *supra* note 66, at 2703-07.

<sup>74</sup> See Liz Kowalczyk, *Drug Trials Branch from Teaching Hospitals: Suburban Doctors Answer Call to Help*, BOSTON GLOBE, Aug. 15, 2000, at C1 (noting the ethical problems that arise when pharmaceutical or biotechnology firms pay doctors fees for each patient they enroll).

<sup>75</sup> See Marilyn Chase, *Mixing Science, Stocks Raises Question of Bias in the Testing of Drugs*, WALL ST. J., Jan. 26, 1989, at A1 (discussing the prevalence of financial ties, such as stock ownership, between researchers and companies in their field of research).

<sup>76</sup> See Thomas Bodenheimer, *Uneasy Alliance: Clinical Investigators and the Pharmaceutical Industry*, 342 NEW ENG. J. MED. 1539, 1543 (2000) (noting that "trials conducted in the commercial sector are heavily tipped toward industry interests").

<sup>77</sup> See Eva Mozes-Kor, *The Mengele Twins and Human Experimentation: A Personal Account*, in THE NAZI DOCTORS AND THE NUREMBERG CODE, *supra* note 68, at 53, 55-57 (1992) (providing a victim's account of the infamous Nazi doctor, Josef Mengele's human experiments).

<sup>78</sup> See generally JAMES H. JONES, *BAD BLOOD* (1981) (presenting a critical account of the Tuskegee Study, a study of the effects of untreated syphilis on black men in Alabama).

<sup>79</sup> See Jeffrey M. Drazen and Greg Koski, *To Protect Those Who Serve*, 343 NEW ENG. J. MED. 1643, 1644 (2000). ("[A]ny financial arrangement that creates a situation in which a clinical investigator might have to choose between what is best for a subject and what is best for the investigator is troublesome."); Bodenheimer, *supra* note 76, at 1541 (noting that clinical investigators have an incentive to design studies with the best

interests.<sup>80</sup> In other words, a researcher's self-interest presents an inherent threat to scientific objectivity.<sup>81</sup>

Several recent, highly-publicized deaths in the course of clinical research protocols have lent an appealing and haunting human face to the hazards inherently associated with experimental research on human beings. Most prominent was the sudden death of Jesse Gelsinger in the course of a Phase One gene transfer trial, referenced earlier in this article.<sup>82</sup> The subsequent investigation into Jesse's tragic and unnecessary death revealed both substantial financial conflicts of interest among the clinical investigators, and inadequate protection for the human subjects of that research protocol. These flaws persisted, notwithstanding that the study was conducted in an academic environment where a great deal of cutting-edge research involving human subjects takes place.<sup>83</sup> This tragedy and others in turn have generated pleas for significantly heightened oversight of all clinical trials.

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chances of positive results because drug manufacturers will often refuse to fund those whose results might reduce sales of their drugs).

<sup>80</sup> See Bodenheimer *supra* note 76, at 1541 (noting that financial interests may force the investigator to choose between what is best for the patients and what is best for the investigator).

<sup>81</sup> See Baruch A. Brody, *Conflicts of Interests and the Validity of Clinical Trials*, in CONFLICTS OF INTEREST IN CLINICAL PRACTICE AND RESEARCH, 407, 413 (Roy G. Spece et al., eds. 1996) (arguing that conflicts of interest arise when controversial decisions must be made by researchers who may be biased by financial interests); Bernard Lo et al., *Conflict-of-Interest Policies for Investigators in Clinical Trials*, 343 NEW ENG. J. MED. 1616, 1619 (2000) (stating that because bias may occur at any stage of a clinical trial, financial interests should be prohibited at all stages).

<sup>82</sup> See Theodore Friedmann, *Principles for Human Gene Therapy Studies*, 287 SCIENCE 2163, 2163 (2000) (observing that Gelsinger's death was the catalyst for increased focus on human gene therapy studies); Donna Shalala, *Protecting Research Subjects - What Must Be Done*, 343 NEW ENG. J. MED. 808 (2000).

<sup>83</sup> See Joseph B. Martin and Dennis L. Kasper, *In Whose Best Interest? Breaching the Academic-Industrial Wall*, 343 NEW ENG. J. MED. 1646, 1649 (2000) (arguing for mandatory oversight committees any time an academic institution conducts clinical research involving human subjects).

The increasingly and embarrassingly public difficulties associated with physician conflicts of interest in clinical research have become so acute that the Secretary of Health and Human Services (HHS), The National Institutes of Health (NIH), the Centers for Disease Control (CDC), and the Food and Drug Administration (FDA) co-sponsored a “Conference on Human Subject Protection and Financial Conflict of Interest” in the summer of 2000.<sup>84</sup> Newly-appointed director-designate of the Office for Human Research Protection, Dr. Greg Koski, remarked in a plenary session on the magnitude of physician conflicts of interest and drew widespread media attention.<sup>85</sup> Dr. Koski cautioned the 700 attendees that financial conflicts of interest in research have “gotten entirely out of control,” and that the currently-required disclosure of federally-funded investigator conflicts only to the institutions under whose aegis they conduct their research is no longer sufficient.<sup>86</sup> The conference reportedly reached a loose consensus that something definitive must be done to minimize financially-induced bias in scientific research.

Current federal rules require federally-funded clinical investigators and applicants for approval of new drugs, biological products or medical devices, whose submission relies in part on clinical data, to disclose “. . . financial arrangements between

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<sup>84</sup> For an agenda of the conference, see *Conference on Human Subject Protection and Financial Conflict of Interest, Agenda* (last modified Aug. 8, 2000) at <<http://aspe.hhs.gov/sp/coi/agenda.htm>>. For a comprehensive report on that conference, see Mark Barnes and Sara Krauss, *Conflicts of Interest in Human Research: Risks and Pitfalls of “Easy Money” in Research Funding*, 9 BUREAU NAT’L AFF. 1378 (Aug. 31, 2000).

<sup>85</sup> See, e.g., Philip J. Hilts, *Medical-Research Official Cites Ethics Woes*, N.Y. TIMES, Aug. 17, 2000, at A20 (reporting on Dr. Koski’s comments at the conference).

<sup>86</sup> See *Conference on Human Subject Protection and Financial Conflicts of Interest, Aug. 16, Plenary Presentation* (visited January 19, 2001) <<http://aspe.hhs.gov/sp/coi/8-16.html>>; see also Emmanuel, *supra* note 66, at 2701 (discussing the seven ethical requirements for clinical research and stating that informed consent alone is insufficient).

sponsor(s) of the covered studies and the clinical investigators and . . . interests of the clinical investigators in the product under study or in the sponsor of the covered studies.”<sup>87</sup> The federal rules mandate clinical investigators to report any potential conflicts of interest to the institutions sponsoring their studies.<sup>88</sup> The sponsoring institutions are then required to assure the FDA that all potential conflicts have been “managed, reduced, or eliminated.”<sup>89</sup> Significantly, the rules do not require the investigator to disclose conflicts to human subjects or to the government unless the institution cannot assure that the conflict has been “managed.” This is an astonishingly loose standard. In any jurisdiction adopting the common law rule requiring disclosure of researcher financial conflicts of interest set forth in the widely-cited case of *Moore v. Regents of California*,<sup>90</sup> the clinician who fails to disclose financial conflicts to patients is nonetheless at her peril for common law tort liability.<sup>91</sup> The federal rules currently do nothing to insure that an investigator's non-financial conflicts of interest do not taint human subject research. They are completely silent on the subject of non-financial conflicts.

#### IV. Conclusion

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<sup>87</sup> 21 C.F.R. §54.1 (2000)

<sup>88</sup> *See id.* at §54.4.

<sup>89</sup> *See* Frequently Asked Questions Concerning the Department of Health and Human Services Objectivity in Research Regulations and the National Science Foundation Investigator Financial Disclosure Policy, 61 Fed. Reg. 34,839, 34,840 (1996) (stating that the Public Health Service rules require institutions to report all potential conflicts of interest, and to provide assurances that conflicts have been “managed, reduced or eliminated,” while the National Science Fund rules requires institutions to report only those conflict that have not been “managed, reduced or eliminated”).

<sup>90</sup> 793 P.2d 479 (1990).

<sup>91</sup> *See id.* at 483-85 (holding that performing medical procedures without informed consent is a breach of a doctor’s fiduciary duty of care).

Trust is the *sine qua non* for public support of medical research. Clinical investigations inevitably subject human participants to the risk of harm in order to produce scientific results designed to advance the social good.<sup>92</sup> Research subjects must *trust* that those risks have been limited to an irreducible minimum, and that the potential consequences of their participation have been completely explained to them, before they assume the status of experimental animals.<sup>93</sup> Without that trust, societal support for human participation in clinical trials will simply vanish - or ought to. Civilized society's deeply-rooted ethical and legal traditions of respect for the autonomy of human beings demands no less.<sup>94</sup>

Phase One trials of new drugs and devices specifically evaluate the risks of innovative clinical interventions, before ever addressing questions of efficacy.<sup>95</sup> When, in Phase Two studies, clinical investigators' evaluative focus officially switches to efficacy, the examiners must still remain alert to issues of safety.<sup>96</sup> Finally, in Phase Three trials, researchers explicitly monitor safety and efficacy in tandem to gauge risk/benefit response to the intervention across large populations.<sup>97</sup> At each of these stages, the human subjects should be entitled, at the very least, to information regarding any special factors that might distort the investigator's objectivity and unnecessarily

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<sup>92</sup> Cf. Samuel Hellman & Deborah S. Hellman, *Of Mice But Not Men: Problems of the Randomized Clinical Trial*, 324 NEW ENG. J. MED 1585 (1991) (stating that the role of the clinical scientist is to answer questions, not treat patients).

<sup>93</sup> See generally Beverly Woodward, *Challenges to Human Subject Protections in US Medical Research*, 282 JAMA 1947 (1999) (noting the need for increased commitment to safeguard human subjects in light of increased human subject research).

<sup>94</sup> The fifth Basic Principle of the Declaration of Helsinki states that, "[c]oncern for the interests of the subject must always prevail over the interest of science and society." Declaration of Helsinki II, *supra* note 68, at 332.

<sup>95</sup> See *supra* note 6 (describing Phase One clinical studies).

<sup>96</sup> See *id.* (describing Phase Two clinical studies).

<sup>97</sup> See *id.* (describing Phase Three clinical studies).

compromise their health status. A clinical investigator's significant financial interest in the drug, biologic agent, or device being evaluated in an experimental trial is such a special factor. Most people would consider knowledge of the divided loyalties such an economic conflict engenders to be material to their informed consent to participate in the study.

Current federal regulations do not require investigators to disclose their direct financial conflicts of interest to human subjects,<sup>98</sup> and few - if any - institutions mandate that such information be conveyed to them. Today, only a few institutions, but not the federal government,<sup>99</sup> prohibit clinical researchers having significant equity interests in the products they evaluate from conducting trials on human subjects. According to a recent study, Harvard Medical School is the only academic institution placing absolute limits on economic conflicts of interest between its researchers and the human subjects of clinical trials.<sup>100</sup> Members of the Harvard medical faculty may not conduct research in academic laboratories or teaching hospitals for companies in which they hold more than \$20,000 worth of stock, or from which they receive more than \$10,000 in consulting fees or royalties.<sup>101</sup>

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<sup>98</sup> See text accompanying note notes 87-90 (discussing the scope of federal regulation of clinical studies).

<sup>99</sup> See S. Van McCrary et al., *A National Survey of Policies on Disclosure of Conflicts of Interest in Biomedical Research*, 343 NEW ENG. J. MED. 1621 (2000) (noting that the U.S. Public Health Service and National Science Foundation do not require research institutions to report investigator financial conflicts of interest to the funding agency - let alone to patients - but permit "internal management" of such conflicts instead).

<sup>100</sup> See Bernard Lo et al., *Conflict-of-Interest Policies for Investigators in Clinical Trials*, 343 NEW ENG. J. MED. 1616, 1619 (2000). (analyzing conflict-of-interest policies at the ten U.S. medical schools receiving the most NIH research funding).

<sup>101</sup> See Richard A. Knox, *Harvard Won't Ease Research Standards: Medical School Stands by Conflict Rules*, BOSTON GLOBE, May 26, 2000, at A1.

Dean Joseph Martin of the Harvard Medical School decided not to relax Harvard's restrictions after serving as a member of the panel convened to investigate Jesse Gelsinger's death.<sup>102</sup> In an article published in the *New England Journal of Medicine*, Dr. Martin clearly and publicly set forth his position that researchers should not receive secondary income from the results of their research on human subjects.<sup>103</sup> "Research in which new drugs, biologic agents, or medical devices are tested in patients must be performed in such a way that there is no possibility - or even perception - that the investigators' judgment is clouded by the prospect of financial gain."<sup>104</sup> Dr. Martin averred that disclosure - even to research subjects themselves - will not sufficiently safeguard the subjects' interests.<sup>105</sup> Instead, he proposes to prohibit economic conflicts beyond the *de minimus* level.<sup>106</sup> Most recently, the American Society of Gene Therapy went even further than Dr. Martin, taking the position that its gene therapy researchers should own no equity, stock options or other interests in the companies whose products they are evaluating through clinical trials.<sup>107</sup>

The National Bioethics Advisory Commission<sup>108</sup> (NBAC) focused squarely on investigator financial conflicts of interest in a recent draft report, advocating major

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<sup>102</sup> See *id.*; see also *supra* notes 15-17 and accompanying text (discussing the events surrounding Gelsinger's death).

<sup>103</sup> See Joseph B. Martin & Dennis L. Kasper, *In Whose Best Interest? Breaching the Academic-Industrial Wall*, 343 *NEW ENG. J. MED.* 1646, 1647 (2000).

<sup>104</sup> See *id.*

<sup>105</sup> Dr. Martin *implied* that disclosure alone is insufficient because he suggested a three tiered system of disclosure, monitoring, and exception granting. See *id.* at 1649.

<sup>106</sup> See *id.*

<sup>107</sup> See Mark Barnes and Sara Krauss, *Conflicts of Interest in Human Research: Risks and Pitfalls of "Easy Money" in Research Funding*, 9 *BNA HEALTH L. REP.* 1378, 1378 (2000).

<sup>108</sup> The NBAC was created by President Clinton's Executive Order 12975. See 60 *Fed. Reg.* 52063 (1995).

revisions to the fragmented federal regulation of human-subject research.<sup>109</sup> The NBAC took the position that prohibiting financial conflicts altogether is unfeasible in view of industry's increasing financial support for the research enterprise<sup>110</sup> and government support for a more streamlined technology transfer to the marketplace.<sup>111</sup> On the other hand, the report found that mere disclosure of financial conflicts will not sufficiently protect human subjects.<sup>112</sup> The Commission took the middle road and recommended better "management" of financial conflicts by "sponsors"<sup>113</sup> and "institutions"<sup>114</sup> of clinical research.<sup>115</sup> The NBAC also recommended that Congress establish a National Office of Human Research Oversight to oversee all research involving human subjects,<sup>116</sup> and that it "issue guidance defining conflicts of interest and ways to ensure that these conflicts do not subject research participants to any *unnecessary* harm."<sup>117</sup>

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<sup>109</sup> See National Bioethics Advisory Commission, *Ethical and Policy Issues in Research Involving Human Participants*, Chapter 4, 18-21 (Dec. 19, 2000) (draft report, available at <[http://bioethics.gov/human/humanpdf\\_toc.html](http://bioethics.gov/human/humanpdf_toc.html)>).

<sup>110</sup> Federal government support for medical research nearly doubled (from \$6.9 billion to \$13.4 billion) in the decade between 1986 and 1995, while industry expenditures tripled (from \$6.2 billion to \$18.6 billion) in the same period. See *id.* at 4. (suggesting that there has been phenomenal growth in federal and industry sponsored research).

<sup>111</sup> See, e.g., 35 U.S.C. §202 (2000) (giving recipients of government grants the title to inventions that result from such funding).

<sup>112</sup> See National Bioethics Advisory Commission, *supra* note 109, at 20.

<sup>113</sup> See *id.*, Chapter 2, at 13 (defining sponsors as the government or private organizations that fund research).

<sup>114</sup> See *id.*, Chapter 2, at 12 (defining institutions as organizations that employ investigators, or on whose premises research takes place).

<sup>115</sup> See *id.*, Recommendation 4.9, Chapter 4, at 26 ("Sponsors and institutions should . . . manage all types of conflicts of interest but especially financial conflicts.").

<sup>116</sup> See *Id.* Chapter 2, at 21 ("Creation of the independent, single office would require federal legislation bring [sic] it into existence and to empower it with specific authorities . . . .")

<sup>117</sup> *Id.*, Recommendation 4.7, Chapter 4, at 25 (emphasis added).

The report's frank, if highly truncated, discussion of financial conflicts is refreshing, but its recommendations leave much to be desired.<sup>118</sup> The NBAC concedes that researcher and institutional monetary conflicts cannot be eliminated, but refrains from compelling disclosure of those conflicts to human subjects. The Commission recommends only that researchers should disclose their conflicts to participants "when appropriate."<sup>119</sup> The entity evaluating "appropriateness" is to be the relevant institutional IRB, whose traditionally overworked members must recuse themselves from reviewing research protocols in which they themselves have conflicts.<sup>120</sup> Although the report takes a significant step by requiring researchers to disclose conflicts to IRBs as a matter of course, rather than merely being "managed in house" by the institution, the draft proposal as it stands is inadequate. Institutions and their IRBs will predictably develop a range of inconsistent approaches to reducing the detrimental impact of conflicts of interest if the projected Office of Research Oversight is empowered only to issue "guidance" defining conflicts and appropriate methods for managing them. Conflicts of economic interest between doctor and patient lend themselves better than most complex problems to fairly precise definition and relatively clear-cut ameliorative response. The government should take a strong leadership role in setting uniform standards for minimizing such financial conflicts, if not eliminating them altogether.

Given burgeoning and increasingly commercial ties between clinical researchers and drug and manufacturing companies, the current *laissez faire* approach toward financial conflicts of interest cannot be defended. Clinical investigators should not

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<sup>118</sup> See *id.*, Chapter 4, at 18-26.

<sup>119</sup> *Id.*, Chapter 4, Recommendation 4.9, at 26.

<sup>120</sup> See *id.*, Chapter 4, at 21. (“[N]o IRB member [may] participate in the review of ‘any project in which the member has a conflicting interest.’”)

realize substantial secondary income because they hold equity interests in the inventions they test on human subjects - to assume otherwise clouds not only scientific objectivity, but public trust as well. The Harvard Medical School policy flatly prohibiting such conflicts in excess of a "nominal" amount is the preferable model, although one could quibble about the best definition of a "nominal" sum.<sup>121</sup>

A researcher's significant financial conflicts constitute material information which, absent compelling circumstances, the researcher ought to disclose to human subjects as a matter of course. This information is vital to the subject's informed consent to serve as a subject of clinical research. Disclosure of such information will not deter most potential subjects from participating in clinical trials, because the medical profession still enjoys a high degree of trust from most people- whether warranted or not.<sup>122</sup> Nonetheless, disclosure, pays the respect that is due to the autonomy of human subjects. Trust between research physicians and patients is a precious commodity, which must not be squandered in the ephemeral pursuit of commerce - or even science.

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<sup>121</sup> See *supra* notes 100-01 and accompanying text (discussing Harvard's ban on certain conflicts).

<sup>122</sup> Cf. TALCOTT PARSONS, *THE SOCIAL SYSTEM* 428-80 (1951); S.L. Murrany et al., *The Benefits of Positive Illusions: Idealization and the Construction of Satisfaction in Close Relationships*, 70 *J. PERS. SOC. PSYCH.*, 79-98 (1998) (observing that cognitive dissonance makes patients with high trust more likely to perceive physician performance positively, even when it is objectively inferior).