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# Bioethical Malpractice: Risk and Responsibility in Human Research

**Erratum**

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# ARTICLES

## BIOETHICAL MALPRACTICE: RISK AND RESPONSIBILITY IN HUMAN RESEARCH

BARBARA A. NOAH\*

*If we knew what it was we were doing, it would not be called research, would it?*

—Albert Einstein (1879-1955)

### I. INTRODUCTION

In the past decade, the pace of medical research involving human subjects has accelerated substantially,<sup>1</sup> promising the development of new treatments that extend life, improve its quality, and prevent disease. Estimates suggest that about seven million people participate in clinical trials funded by the National Institutes of Health (NIH) and another twelve million subjects participate in private trials annually.<sup>2</sup> Looking ahead into the new millennium, the rapidly evolving sciences of genetics and proteomics, along with the continued development of traditional therapies, offer the hope of treatment or cure for currently untreatable illnesses, and ultimately may transform the practice of medicine.<sup>3</sup>

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<sup>1</sup> See Editorial, *Fifty Years of Randomized Controlled Trials*, 317 BRIT. MED. J. 1165 (1998) (describing the history and evolution of the clinical trial); Susan Okie, *U.S. Oversight Urged for Human Research*, WASH. POST, May 16, 2001, at A10 (noting the “explosive growth” of biomedical research, including an increase in federal spending for health research from \$6.9 billion to \$13.4 billion between 1986 and 1995 and an increase in industry research spending from \$6.2 billion to \$18.6 billion during the same time period). Estimates suggest that between 45,000 and 50,000 researchers currently conduct clinical trials in the United States. *Id.*; see also Eve E. Slater, *IRB Reform*, 346 NEW ENG. J. MED. 1402 (2002) (noting that federal funding for clinical research has more than doubled since 1995).

<sup>2</sup> Dan Vergano, *Drug-Trial Deaths 'Go Unreported'*, USA TODAY, Nov. 8, 2000, at D12.

<sup>3</sup> Lars Noah, *The Coming Pharmacogenomics Revolution: Tailoring Drugs to Fit Patients' Genetic Profiles*, 43 JURIMETRICS J. 1, 2-3, 7-10 (2002).

Clinical research provides the necessary bridge from scientific theory to practical medical application,<sup>4</sup> but research involving human subjects sometimes exacts a high price from those who participate. Patients who enroll in therapeutic research protocols take risks, sometimes unwittingly, that they might not ordinarily tolerate in the clinical setting. Healthy volunteers, motivated by altruism or a desire to make money, also encounter risks when they agree to participate in non-therapeutic research designed to advance scientific understanding. The medical community often assumes, perhaps over-optimistically, that clinical research enhances scientific knowledge in ways that ultimately will benefit many patients.<sup>5</sup> Sometimes, experimental protocols actually benefit research subjects directly. Other times, however, as with the recent deaths of several research participants, hindsight suggests that no amount of improved scientific understanding or medical benefit appears to justify the risks of a particular research plan.

Recent events have drawn public attention to flaws in the regulatory system that is designed to protect human research subjects and have prompted demands for reform.<sup>6</sup> Although calculating the number of research-related deaths and injuries has proven difficult, one expert suggests that as many as 5,000 people die annually in federally-funded research protocols, while tens of thousands more suffer injuries.<sup>7</sup> Injuries in privately-funded research remain even more difficult to estimate due to the lack of any unified tracking system.

Institutional review boards (IRBs), the entities charged with the task of protecting human research subjects from coercion and unreasonable risk, suffer from significant limitations that impede their mission. The United States General Accounting Office (GAO) and the Department of Health and Human Services (HHS) have sounded the alarm, issuing highly critical reports about the ineffectiveness of IRBs.<sup>8</sup> Federal regulatory agencies and state health policy

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<sup>4</sup> See Lars Noah, *Medicine's Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community*, 44 ARIZ. L. REV. 373, 382-95 (2002).

<sup>5</sup> See Roger N. Rosenberg, *Translating Biomedical Research to the Bedside*, 289 JAMA 1305, 1305 (2003) (questioning the "assumption that the recent exponential growth of scientific information about disease . . . heralds a rapid move to improve human health").

<sup>6</sup> See, e.g., Sheryl Gay Stolberg, *Committee Considers Change in Reporting on Gene Therapies*, N.Y. TIMES, Dec. 11, 1999, at A13.

<sup>7</sup> Tom Pelton, *Medical Experiment Disclosure Hinges on a Flawed Honor System*, BALT. SUN, Aug. 12, 2001, at A1 (reporting the conclusions of Adil E. Shamoo, a University of Maryland biochemist who edits the journal *Accountability in Research*, and noting that other experts disagree with Shamoo's estimates because of the difficulty of measuring underreporting).

<sup>8</sup> The HHS Office of the Inspector General (OIG) recently issued a series of reports that criticized the operation of IRBs and Office of Human Research Protection's supervision of human research more generally. The reports focused on several problems endemic to IRB operations, such as overwhelming workload, lack of expertise, and conflicts of interest that interfered with proper review of research protocols. See OFFICE OF INSPECTOR GEN., PUB. NO. OEI-01-97-00193, HHS, INSTITUTIONAL REVIEW BOARDS: A TIME FOR REFORM (1998), available at <http://oig.hhs.gov/oei/reports/oei-01-97-00193.pdf> (last visited July 1, 2004) [hereinafter "HHS Report"]; GAO, PUB. NO. GAO/HEHS-96-72, SCIENTIFIC

bodies also have increased their scrutiny of research activities.<sup>9</sup> HHS's Office for Human Research Protections (OHRP) temporarily suspended research under the supervision of IRBs at more than a dozen research institutions because of non-compliance with regulatory requirements,<sup>10</sup> and it continues to criticize the conduct of specified trials.<sup>11</sup> In several of these cases, the suspension followed the death or serious injury of a patient or healthy volunteer.

In 1999, eighteen-year-old Jesse Gelsinger, a young man with a fairly mild form of an inherited liver disease, volunteered for a gene therapy protocol at the University of Pennsylvania, hoping to improve his condition and to provide scientific information that might be useful in treating infants born with a more severe form of the disease.<sup>12</sup> After receiving a massive dose of a viral vector designed to deliver healthy genes to his liver cells, Mr. Gelsinger developed multiple-organ failure and died.<sup>13</sup> Subsequent investigation revealed that the Recombinant DNA Advisory Committee (RAC), an NIH committee charged with the oversight of all federally-funded gene therapy research, had approved the study notwithstanding some reservations about performing the risky procedure on patients who were coping relatively well with the disorder.<sup>14</sup> Worse still, it later became apparent that the consent form given to Mr. Gelsinger failed to reveal that similar studies had caused deaths in monkeys, or that two other people who had received the viral vector treatment experienced serious side effects.<sup>15</sup> In addition to these gaps in the information conveyed to subjects, the principal investigator

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RESEARCH: CONTINUED VIGILANCE CRITICAL TO PROTECTING HUMAN SUBJECTS 17-19 (1996), available at <http://www.gao.gov/archive/1996/he96072.pdf> (last visited July 1, 2004) [hereinafter "GAO Report"]. The Department followed up with another report that analyzed the extent of implementation of its recommendations. OFFICE OF INSPECTOR GEN., PUB. NO. OEI-01-97-00197, HHS, PROTECTING HUMAN RESEARCH SUBJECTS: STATUS OF RECOMMENDATIONS 2-3 (2000), available at <http://oig.hhs.gov/oei/reports/oei-01-97-00197.pdf> (last visited July 1, 2004) [hereinafter "HHS Status Report"] (concluding that IRBs had made little progress in implementing the recommendations).

<sup>9</sup> See, e.g., Elisabeth Rosenthal, *New York Seeks to Tighten Rules on Medical Research*, N.Y. TIMES, Sept. 27, 1996, at B4 (describing the case of a 19-year-old healthy student volunteer at the University of Rochester who died during a study designed to measure the effects of pollutants on the lungs).

<sup>10</sup> Donald F. Phillips, *IRBs Search for Answers and Support During a Time of Institutional Change*, 283 JAMA 729, 729 (2000).

<sup>11</sup> See Robert Steinbrook, *Trial Design and Patient Safety—The Debate Continues*, 349 NEW ENG. J. MED. 629, 629 (2003).

<sup>12</sup> Joanne Silberner, *A Gene Therapy Death*, HASTINGS CENTER REP., Mar.-Apr. 2000, at 6 (explaining that Mr. Gelsinger suffered from ornithine transcarbamylase deficiency, a metabolic disorder that interferes with the normal processing and elimination of ammonia from the body).

<sup>13</sup> *Id.*; see also Joan Stephenson, *Studies Illuminate Cause of Fatal Reaction in Gene-Therapy Trial*, 285 JAMA 2570, 2570 (2001) (describing later research that identified the immune system's reaction to the vector).

<sup>14</sup> See Silberner, *supra* note 12, at 6 (noting that Penn's own IRB had rejected the alternative of performing the research on infants afflicted with a fatal form of the disease because of concerns that parents of such infants would be unable to make an informed decision about the risks and benefits of participating in the experimental protocol).

<sup>15</sup> Silberner, *supra* note 12, at 6.

(PI) in the study neglected to disclose the fact that he was the founder of the company with rights to all treatments developed by his research laboratory,<sup>16</sup> a potential conflict of interest that very well may have affected the family's decision to participate in the study.

The Gelsinger family eventually sued the University of Pennsylvania, the director of the university's bioethics program, and the PI, among others, claiming that the information provided in the informed consent documents was incomplete and that the research team deliberately misled the family about the safety of the protocol by withholding information about previous adverse events associated with the gene therapy procedure.<sup>17</sup> The lawsuit also alleged that the IRB should never have approved the protocol and claimed that the University and the PI inappropriately held equity stakes in a company with a financial interest in the investigational therapy. The suit settled for an undisclosed amount.<sup>18</sup>

In 2001, Ellen Roche, a 24-year old healthy volunteer, died while participating in an NIH-funded study at the Johns Hopkins University School of Medicine designed to understand the physiologic mechanisms of asthma.<sup>19</sup> The non-therapeutic research protocol required volunteers to inhale an unapproved drug

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<sup>16</sup> Silberman, *supra* note 12, at 6. The FDA later debarred the principal investigator, James Wilson, from conducting research with FDA-regulated products on human subjects. Rick Weiss, *FDA Seeks to Penalize Gene Scientist*, WASH. POST, Dec. 12, 2000, at A14; *see also* Rick Weiss & Deborah Nelson, *Methods Faulted in Gene Test Death; Teen Too Ill for Therapy, Probe Finds*, WASH. POST, Dec. 8, 1999, at A1; Letter from Steven A. Masiello, Director, FDA Office of Compliance and Biologics Quality, to James M. Wilson, M.D., Ph.D. (Nov. 30, 2000), available at <http://www.fda.gov/foi/nidpoe/n121.pdf> (last visited July 1, 2004) (initiating proceeding to disqualify Wilson from receiving investigational products for research, and listing violations of FDA regulations including failure to abide by protocol inclusion criteria, failure to protect rights of subjects, failure to adhere to the approved research protocol, failure to obtain approval for protocol modifications, failing to submit accurate reports regarding adverse events, failure to obtain proper informed consent, and record keeping violations).

<sup>17</sup> See Complaint for Estate of Jesse Gelsinger, *Gelsinger v. Trs. of the Univ. of Pennsylvania*, No. 000901885 (Ct. Com. Pl., Phila. Cty., filed Sept. 18, 2000), available at <http://www.sskrplaw.com/links/healthcare2.html> (last visited July 1, 2004).

<sup>18</sup> Rick Weiss & Deborah Nelson, *Penn Settles Gene Therapy Suit*, WASH. POST, Nov. 4, 2000, at A4. Certain named parties in the suit were released from liability under the terms of the settlement. *Id.* Other injured research subjects or their families have filed lawsuits against research institutions. *See, e.g.*, Debbie Goldberg, *Artificial Heart Implant Leads to Suit Over Consent Process*, WASH. POST, Nov. 30, 2002, at A3 (describing a suit by the widow of the fifth recipient of the AbioCor artificial heart against the manufacturer, the hospital and medical school where it was implanted, and the patient advocate who was designated to assist the couple with the consent process); Associated Press, *'39 Experiment on Stuttering Draws Lawsuit*, N.Y. TIMES, Aug. 6, 2003, at A13 (describing a suit by a group of orphans who were "relentlessly belittled" in order to determine whether stuttering was a learned behavior); Susan Carhart, *Woman Contends Manufacturer Liable in Study of Fecal Incontinence Control Device*, 30 PRODUCT SAFETY & LIABILITY REP. (BNA) 542, 542-43 (2002) (describing a lawsuit against a clinical investigator, IRB members, the hospital, and a medical device manufacturer).

<sup>19</sup> Jonathan Bor & Gary Cohn, *Research Volunteer Dies in Hopkins Asthma Study*, BALTIMORE SUN, June 14, 2001, at A1.

called hexamethonium into their lungs to irritate the bronchial linings.<sup>20</sup> After the PI's search of a medical literature database failed to turn up any serious risks associated with the chemical, the university's IRB approved the research. It later became apparent that the investigator's research efforts had missed older published research reporting serious side effects associated with inhalation of the compound.<sup>21</sup>

In addition, although at least one previous study volunteer developed a persistent cough and shortness of breath, the investigator had failed to report the adverse event and continued the research.<sup>22</sup> OHRP suspended all federally-funded research at the Johns Hopkins University,<sup>23</sup> citing numerous deficiencies in the institution's IRB processes in general, and particular problems with the IRB's approval and oversight of the asthma study.<sup>24</sup> Although research subsequently resumed at Hopkins, critics continue to find fault with the University's protection of human subjects.<sup>25</sup>

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<sup>20</sup> Gina Kolata, *Johns Hopkins Death Brings Halt to U.S.-Financed Human Studies*, N.Y. TIMES, July 20, 2001, at A1. After inhaling the chemical, Ms. Roche developed a fever, severe inflammation of the lungs, and organ failure. *Id.* Upon notification of the death, Hopkins suspended the protocol and notified NIH. See Bor & Cohn, *supra* note 19, at A1. NIH sent out an e-mail alert to all IRBs about the death, along with a request that IRBs immediately reassess any protocols under their supervision involving hexamethonium. See Posting of Michael Carome, [caromem@od.nih.gov](mailto:caromem@od.nih.gov) to [mcwirb@mcwirb.org](mailto:mcwirb@mcwirb.org) (June 14, 2001) (copy on file with the author).

<sup>21</sup> See Jonathan Bor & Tom Pelton, *Hopkins Faults Safety Lapses*, BALT. SUN, July 17, 2001, at A1 (reporting that a routine Internet search would have located the older studies). A search for "hexamethonium" on Google, conducted by the author on July 5, 2003, produced the following citation as the first search result: B. Morrison, *Parenteral Hexamethonium in Hypertension*, 1 BRIT. MED. J. 1291 (1953).

<sup>22</sup> See Bor & Pelton, *supra* note 21, at A1 (noting that the consent form for the study failed to mention that the drug was not approved by the FDA and had no currently accepted clinical uses).

<sup>23</sup> See Kolata, *supra* note 20, at A1 (reporting that Hopkins received \$310 million in 2000—more federal research funding than any other university). The OHRP later lifted the suspension, but it imposed additional restrictions on research at Hopkins. See Jonathan Bor & Tom Pelton, *U.S. Eases Constraints on Hopkins*, BALT. SUN, July 24, 2001, at A1 (reporting that OHRP conditioned the reinstatement on a thorough re-review of all approved research protocols and required non-therapeutic protocols to remain suspended until the IRB completed the review).

<sup>24</sup> Letter from Patrick J. McNeilly, Compliance Oversight Coordinator and Michael Carome, Director, Office for Human Research Protections (OHRP), to Edward D. Miller and Chi Van Dang, Johns Hopkins Univ. School of Medicine, and Gregory F. Schaffer, John Hopkins Bayview Medical Center (July 19, 2001), available at [http://www.hhs.gov/ohrp/detrm\\_lettrs/jul01a.pdf](http://www.hhs.gov/ohrp/detrm_lettrs/jul01a.pdf) (last visited July 1, 2004). OHRP lifted the suspension after it received a corrective action plan from the University. *Id.*

<sup>25</sup> See Shankar Vedantam, *Johns Hopkins Faults Researcher in Human Drug Trial*, WASH. POST, Nov. 13, 2001, at A6 (describing violations of human subjects protections in a cancer research protocol in India conducted by a Johns Hopkins researcher); see also Robert Steinbrook, *Protecting Research Subjects: The Crisis at Johns Hopkins*, 346 NEW ENG. J. MED. 716 (2002); Jonathan Bor, *Hopkins Defends Two Studies*, BALT. SUN, Dec. 29, 2001, at B1 (describing criticism of a study of cocaine addiction in which Hopkins paid \$600 - \$700 to cocaine addicts for participation, and a study of childhood hormonal problems in which researchers failed to inform participants of side effects of medications used in the study). In a less-publicized but equally deadly recent event, Elaine Holden-Able, a 70-year-old healthy volunteer suffered cardiac and respiratory arrest and eventually died after

In still another recent incident, patients in a clinical trial of a melanoma vaccine at the University of Oklahoma sued the principal investigator, the manufacturer of the experimental vaccine, and the members of the IRB that approved the study, alleging that the researchers had failed to inform the participants of relevant risks and had misrepresented information in order to obtain government permission to conduct the trial.<sup>26</sup> The nurse coordinator for the study became concerned when she realized that the PI continually enrolled subjects who did not meet the medical inclusion criteria for the approved protocol and that the chair of the IRB routinely approved major deviations from the study procedures retroactively, in clear violation of federal regulations. When the University conducted an audit of the research, it discovered serious safety problems with the manufacture and testing of the vaccine and it shut down the research.<sup>27</sup>

This accumulation of events has real consequences for the future of biomedical research. Already, researchers are encountering growing suspicion from prospective trial participants, and are experiencing increased difficulty in recruiting subjects.<sup>28</sup> Moreover, as these examples illustrate, inappropriate research conduct and flaws in oversight pose risks to human subjects that may

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receiving an apparent overdose of a dietary supplement in a trial at Case Western Reserve University to test its effectiveness in treating Alzheimer's disease. Susan Okie, *A Death During Research: Apparent Supplement Overdose Killed Healthy Volunteer*, WASH. POST, Jan. 12, 2002, at A3 (explaining that a dietary aide working with nurses in the study may have inadvertently given the subject 83 grams rather than 8,300 milligrams of the supplement). Although the University immediately halted the research and conducted an internal review, it did not notify OHRP of the participant's death until four months later. After reviewing the University's report, OHRP closed its investigation without imposing any kind of penalty. Michael Kranish, *System for Protecting Humans in Research Faulted*, BOSTON GLOBE, Mar. 25, 2002, at A1; see also Okie, *supra*, at A3 (noting that Case Western withheld a public announcement of the death for nine months pending an OHRP investigation, which ultimately absolved the University of any wrongdoing). The death in this case appears to have resulted from human error rather than faulty oversight, though perhaps the IRB could have required additional safety measures that would have prevented the accidental overdose. *Id.*

<sup>26</sup> See Edward T. Pound, *Cancer Study Participants Sue Researcher*, USA TODAY, Jan. 30, 2001, at A4. The lawsuit claims that the investigator repeatedly violated federal research regulations, and this appears to be the first suit to name individual members of the IRB as defendants. See Complaint for Dawanna Robertson et al., *Robertson v. McGee*, (N.D. Okla. 2001) (No. 01-CV-60), available at 2002 WL 535045. The University fired the PI and the chair of the IRB, and it received resignations from the dean of the college of medicine and the director of the office of research at the health science center in response to the litigation. *Researchers Face Terminations in Scandal*, CHI. TRIB., July 22, 2000, at A17. The OHRP temporarily shut down all research at the University of Oklahoma. Edward T. Pound & Jessie Halladay, *Tulsa Trials Conditionally Reinstated*, USA TODAY, July 14, 2000, at A3.

<sup>27</sup> Jennifer Washburn, *Informed Consent*, WASH. POST, Dec. 30, 2001, at W16 (reporting that litigation against the University of Oklahoma and its IRB is pending).

<sup>28</sup> Linda Marsa, *Clinical Trials Are Suffering; Suspicious of Medical Research, Volunteers Spurn Tests of Possibly Lifesaving Advances*, L.A. TIMES, Dec. 2, 2002, at F1 (reporting that, in 2001, 86% of clinical trials failed to meet enrollment goals, an increase from 80% of under enrolled trials in 1999). Of course, some research protocols simply lack appeal. See, e.g., Marlene Cimons, *Finally, Science Weighs In*, L.A. TIMES, Mar. 18, 2002, at S1 (describing a five-year, \$1.4 million study to evaluate the effectiveness of an experimental pancreatic cancer regimen that requires two coffee enemas a day).

form the basis for liability actions against IRBs and the institutions that house them. Institutional and investigator failures to comply with basic research regulations certainly contributed to some of the recent injuries, but other less easily remedied flaws in the system of human subjects protection pose even greater challenges. Conscientious compliance with the minimal standards in the federal rules satisfies only a portion of the legal and ethical obligations in clinical research. Because the regulations only provide basic parameters for acceptable research, IRBs and investigators must work harder to interpret and implement the rules appropriately for the myriad individual research plans that they consider.

The changing climate of medical research – particularly pressures arising from increased research volume, the lack of effective training mechanisms, lack of expertise on IRBs in highly specialized fields of medicine, and complex relationships between academic researchers and private funding sources – increases the likelihood that these boards will fail in their mission to protect human subjects. In addition to failures to comply with explicit human subjects protection regulations, IRBs may underestimate risks, miss ethical or scientific deficiencies in the design of research protocols, or make other similar errors of judgment, thereby subjecting unwitting research participants to inappropriate and avoidable jeopardy. IRBs increasingly may face tort liability for what I will call “bioethical malpractice” – a failure to exercise reasonable judgment within the confines of the regulatory scheme governing human subjects research. Although tort claims brought by injured research subjects remain rare, recent events suggest that this type of litigation will increase in frequency.<sup>29</sup> Several lawsuits against IRBs are pending and more will surely follow.

This Article provides an overview of IRB operations, reviews the sources of regulatory guidance, and examines the weaknesses of the existing system for the protection of human research subjects. It then discusses the scant case law relating to IRB negligence in the protection of human research subjects and explores some hypothetical circumstances under which it may be appropriate to hold a board accountable for injuries to clinical trial participants. Finally, this Article considers the potential consequences of expanded IRB liability, concluding that tort law sometimes may serve an important function as a catalyst to regulatory reform when professional self-regulation and governmental supervision fail.

## II. IRB OPERATIONS

Existing federal regulations delegate to IRBs the responsibility to safeguard research subjects who participate in clinical trials of experimental treatments and in non-therapeutic trials designed to gain generalizable scientific knowledge. In order

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<sup>29</sup> See Maureen Milford, *Lawsuits Attack Medical Trials*, NAT'L L.J., Aug. 27, 2001, at A1 (describing how several recent wrongful death actions against well-known medical research institutions have “opened the door” for more accountability in human research).

to protect human research subjects effectively, IRBs must use their combined expertise to assess the scientific, ethical, and legal validity of every proposed research protocol and must continue vigilant monitoring of approved protocols. This Part describes the IRB review and supervision process, and it identifies weaknesses inherent in the regulatory system, exploring the pressures and complexities in IRB operations that may increase the likelihood of avoidable injury to research subjects.

### A. *The Regulatory Framework*

The existing system of human research regulation evolved over time in reaction to a series of publicized incidents of research abuse. The Nuremberg Code, which emerged out of the trials of Nazi physicians after the Second World War,<sup>30</sup> sets out essential principles for permissible medical experiments.<sup>31</sup> In 1964, the World Medical Association adopted the Declaration of Helsinki, which provides additional commentary on the Nuremberg Code.<sup>32</sup> In 1979, in response to several notorious research abuses in the United States, such as the Tuskegee syphilis study,<sup>33</sup> the National Commission for the Protection of Human Subjects

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<sup>30</sup> For information on the development of the Nuremberg Code, see generally ROBERT JAY LIFTON, *THE NAZI DOCTORS: MEDICAL KILLING AND THE PSYCHOLOGY OF GENOCIDE* (1986); *THE NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION* (George J. Annas & Michael A. Grodin eds., 1992); Jeffrey H. Barker, *Human Experimentation and the Double Facelessness of a Merciless Epoch*, 25 N.Y.U. REV. L. & SOC. CHANGE 603 (1999); see also Harold Edgar & David J. Rothman, *The Institutional Review Board and Beyond: Future Challenges to the Ethics of Human Experimentation*, 73 MILBANK Q. 489, 494-97 (1995) (describing the political evolution of the research regulations in the context of the Nuremberg trials and the revelation of various American research abuses).

<sup>31</sup> The Nuremberg Code emphasizes the necessity that research design and conduct assure a genuine quest for societal good and that the patient be fully informed at all times during participation, and at complete liberty to remove him or herself from participation. See DIRECTIVES FOR HUMAN EXPERIMENTATION: NUREMBERG CODE, TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW No. 10, Vol. 2, at 181-182 (Gov't Printing Office 1949); see also Jay Katz, *Human Sacrifice and Human Experimentation: Reflections at Nuremberg*, 22 YALE J. INT'L L. 401, 413-17 (1997) (commenting on problematic aspects of the Code's implementation).

<sup>32</sup> WORLD MED. ASS'N, DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (2002), available at <http://www.wma.net/e/policy/b3.htm> (last visited July 1, 2004). See also COUNCIL FOR INT'L ORGS. OF MED. SCIENCES, INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (2002), available at [http://www.cioms.ch/frame\\_guidelines\\_nov\\_2002.htm](http://www.cioms.ch/frame_guidelines_nov_2002.htm) (last visited July 1, 2004); Beverly Woodward, *Challenges to Human Subject Protections in US Medical Research*, 282 JAMA 1947, 1948-49 (1999) (describing ongoing efforts to revise international guidelines, sometimes in ways that emphasize scientific progress over the individual interests of human subjects).

<sup>33</sup> See generally FRED D. GRAY, *THE TUSKEGEE SYPHILIS STUDY: THE REAL STORY AND BEYOND* (1998); JAMES H. JONES, *BAD BLOOD: THE TUSKEGEE SYPHILIS EXPERIMENT* (1993).

issued the Belmont Report.<sup>34</sup> Finally, the American Medical Association (AMA) has published a variety of opinions dealing with ethical issues in clinical research.<sup>35</sup>

These ethical codes and guidelines provided the underpinnings for today's federal oversight regime. In 1974, the Department of Health, Education, and Welfare (HEW, the predecessor of HHS) promulgated the first formal regulations governing human research.<sup>36</sup> Seven years later, the Food and Drug Administration (FDA) issued its own regulations.<sup>37</sup> Both the OHRP and the FDA have the authority to inspect records and suspend research activities at institutions that receive federal funding.<sup>38</sup> IRBs represent a central feature of this system, and they have become widespread, with an estimated 3,000 to 5,000 such boards now operating in academic medical centers, hospitals, and at government agencies like NIH.<sup>39</sup> More recently, independent boards that review and monitor research for a

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<sup>34</sup> See Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 44 Fed. Reg. 23,192 (1979) (emphasizing and expanding on principles of informed consent and protection of vulnerable research subjects).

<sup>35</sup> See, e.g., Am. Med. Ass'n, *Subject Selection for Clinical Trials* (E-2.071), available at <http://www.ama-assn.org/ama/pub/category/8423.html> (last visited July 1, 2004); Am. Med. Ass'n, *The Use of Placebo Controls in Clinical Trials* (E-2.075), available at <http://www.ama-assn.org/ama/pub/category/8424.html> (last visited July 1, 2004); Am. Med. Ass'n, *Managing Conflicts of Interest in the Conduct of Clinical Trials* (E-8.0315), available at <http://www.ama-assn.org/ama/pub/category/8471.html> (last visited July 1, 2004).

<sup>36</sup> 39 Fed. Reg. 18914 (May 30, 1974) (codified as amended at 45 C.F.R. pt. 46 (2003)). These regulations were later extended to apply to other federal agency supported research. The research community now commonly refers to the HHS regulations as the "Common Rule." See NAT'L BIOETHICS ADVISORY COMM'N, ETHICAL AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS VOL. 1, 156 (2001), available at <http://www.georgetown.edu/research/nrcbl/nbac/human/overvol1.pdf> (last visited July 1, 2004).

<sup>37</sup> Protection of Human Subjects; Informed Consent, 46 Fed. Reg. 8942 (Jan. 27, 1981) (codified as amended at 21 C.F.R. pts. 50 & 56 (2003)); see also 46 Fed. Reg. 8366 (Jan. 26, 1981) (codified as amended at 54 C.F.R. pt. 46 (2003)) (amending HHS regulations to expand upon the original research policy and exempt certain types of minimal risk research from IRB review). In addition to the two sets of federal regulations, several states have promulgated laws to protect human research subjects. See, e.g., CAL. HEALTH & SAFETY CODE §§ 24170-24179 (1992); FLA. STAT. ANN. § 381.026(4)(e) (2001); N.Y. PUB. HEALTH LAW §§ 2440-2446 (2002); VA. CODE ANN. § 32.1-162.16 to .20 (2001); see also Maria Woltjen, *Regulation of Informed Consent to Human Experimentation*, 17 LOY. U. L.J. 507, 518-23 (1986) (surveying earlier state statutes).

<sup>38</sup> 21 C.F.R. § 56.115(b) (2003) (permitting FDA inspection, review, and copying of IRB records). When FDA inspectors disqualify a researcher or a research institution, the regulations permit the suspension of ongoing research protocols. *Id.* at § 56.121. The FDA has the authority to disqualify clinical investigators from receiving investigational products for research purposes. See *id.* pt. 16.1. When an institution or its investigators fail to comply with HHS human subject policies, the funding agency may terminate or suspend research support. 45 C.F.R. § 46.123(a) (2003).

<sup>39</sup> HHS Report, *supra* note 8, at 3; Robert Steinbrook, *Improving Protection for Research Subjects*, 346 NEW ENG. J. MED. 1425, 1425 (2002). The fact that the Office of the Inspector General, which prepared the HHS reports, was unable to produce a more accurate estimate of the total number of IRBs in operation nicely illustrates the lack of systematic oversight of their activities.

fee have emerged.<sup>40</sup> The discussion that follows focuses primarily on IRBs in academic medical centers and hospitals, though independent IRBs suffer from many of the same problems as well as some additional complexities peculiar to the for-profit model.<sup>41</sup>

The federal rules apply to most, though not all, clinical research conducted in the United States. The FDA regulations apply to all human subjects research involving articles such as drugs, medical devices, and biological products that eventually will support a licensing application to the agency,<sup>42</sup> while the HHS regulations cover all research conducted or supported by the federal government.<sup>43</sup> All institutions receiving HHS funding must provide the Department with assurances that every project conducted at the institution, regardless of the source of funding, will abide by the human subjects protection regulations.<sup>44</sup>

These two overlapping sets of federal research regulations provide a wealth of detail about standards for approval and supervision of human research.<sup>45</sup>

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<sup>40</sup> HHS regulations require that all federally-sponsored research be monitored by local boards. See 45 C.F.R. §46.102-103 (2003). Thus, these freestanding IRBs usually monitor privately-sponsored research. The fact that the review is fee-based raises questions about the level of scrutiny accorded to such research. See Karine Morin et al., *Managing Conflicts of Interest in the Conduct of Clinical Trials*, 287 JAMA 78, 79 (2002) (observing that, “[a]lthough some commentators have argued that independent boards conduct their reviews more efficiently than IRBs affiliated with academic medical centers, others have expressed concerns that independent boards face financial conflicts of interest since their very existence depends on the continuous flow of protocols to review, which may lead them to use less stringent standards”); see also Trudo Lemmens & Benjamin Freedman, *Ethics Review for Sale? Conflict of Interest and Commercial Research Review Boards*, 78 MILBANK Q. 547, 548-49 (2000) (describing how the rapid growth in drug and other medical research led to the proliferation of commercial boards, which purport to provide “efficient” IRB review).

<sup>41</sup> See OFFICE OF INSPECTOR GEN., PUB. NO. OEI-01-97-00192, HHS, INSTITUTIONAL REVIEW BOARDS: THE EMERGENCE OF INDEPENDENT BOARDS (1998), available at <http://www.researchroundtable.com/pdffiles/irbemergence.pdf> (last visited July 1, 2004) (describing the role of independent institutional review boards in ensuring protections for human subjects of clinical research).

<sup>42</sup> 21 C.F.R. § 50.1 (2003).

<sup>43</sup> 45 C.F.R. § 46.101 (2003). Many sections of the FDA and HHS regulations are nearly identical. For a useful comparison between the two sets of regulations, see FDA, COMPARISON OF FDA AND HHS HUMAN SUBJECT PROTECTION REGULATIONS, available at [www.fda.gov/oc/gcp/comparison.html](http://www.fda.gov/oc/gcp/comparison.html) (last visited July 1, 2004). This Article will cite the HHS regulations except in cases where the FDA regulations differ significantly; in those cases, both sets of regulations will be cited.

<sup>44</sup> 45 C.F.R. § 46.103 (2003).

<sup>45</sup> IRBs cannot monitor research unless the investigator requests approval and performs the research activities within the bounds of the approved protocol. In one case, the investigator bypassed the IRB review process altogether and used his corneal transplant surgical device on several patients without informing them that the device and the procedure were experimental and not approved by the FDA. Two of those patients whose surgery was unsuccessful sued, alleging that the investigator breached his duty to obtain their informed consent. The experimental surgeries, conducted by the chair of the University of South Florida’s Department of Ophthalmology, were not supervised by the University’s IRB, although the board had approved a separate clinical trial with an informed consent document that described the investigational device and explained that the trial was intended to test its safety and effectiveness. Instead, the investigator operated on patients outside of the approved protocol, claiming

Nevertheless, the regulations leave some of the most difficult scientific issues unresolved, and they leave important ethical questions to the discretion of IRBs, which may vary substantially in their interpretation and application of the regulatory requirements. In effect, the federal government has deputized these boards, delegating to private groups composed of relevant experts primary responsibility for applying the rules.<sup>46</sup> Thus, variations in IRB workload, institutional support and resources, and attitudes towards the informed consent process can lead to significant differences in the implementation of the federal regulations among boards, thereby potentially compromising this core mission.<sup>47</sup>

### 1. *Review of New Research Protocols*

With few exceptions, all new research protocols involving human subjects require full board review.<sup>48</sup> The regulations which set out criteria for approval require the IRB to assess a variety of scientific and ethical factors. First, the study design must minimize the risks to the subjects by using sound research procedures and, in the case of therapeutic research, by preferring procedures that typically

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that he was providing standard therapy. Ultimately, doctors in the investigator's department brought the case to the attention of the University's administration, expressing concern that the investigator had violated human subjects protections regulations. See Edward T. Pound, *Federal Rules for Research on People Often Fail*, USA TODAY, Feb. 26, 2001, at A1.

<sup>46</sup> See Lars Noah, *Deputizing Institutional Review Boards to Police (Audit?) Biomedical Research*, 25 J. LEGAL MED. (forthcoming Sept., 2004). For a discussion of the strengths and weaknesses of this strategy in other contexts, see Lars Noah, *Scientific "Republicanism": Expert Peer Review and the Quest for Regulatory Deliberation*, 49 EMORY L.J. 1033 (2000).

<sup>47</sup> See JESSICA W. BERG ET AL., INFORMED CONSENT: LEGAL THEORY AND CLINICAL PRACTICE 259 (2d ed. 2001); Carl H. Coleman, *Rationalizing Risk Assessment in Human Subjects Research*, 46 ARIZ. L. REV. 1 (2004). See also Jerry Goldman & Martin D. Katz, *Inconsistency and Institutional Review Boards*, 248 JAMA 197, 198-99 (1982) (analyzing how 22 different IRBs reviewed identical research protocols; and reporting substantial inconsistency among boards in the application of both regulatory requirements for informed consent and ethical principles); Rita McWilliams et al., *Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study*, 290 JAMA 360, 364-65 (2003) (evaluating the review by 31 different IRBs of a multicenter cystic fibrosis genetic study, and concluding that the highly variable approaches of different boards compromised human subjects protection and created inefficiencies).

<sup>48</sup> The regulations exempt certain types of human subjects research from IRB review. See 45 C.F.R. §46.101(b) (2003) (exempting educational research, surveys, interviews, observation of public behavior, educational aptitude tests, and certain types of research designed to evaluate public benefit programs). The regulations exempt taste and food quality evaluations and consumer acceptance studies of foods. *Id.*; see also Lars Noah & Richard A. Merrill, *Starting from Scratch?: Reinventing the Food Additive Approval Process*, 78 B.U. L. REV. 329, 376-77 (1998). Another regulation permits expedited review of certain research involving no more than minimal risk and of minor changes in approved research protocols. 45 C.F.R. § 46.110 (2003). The regulations define "research" as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." *Id.* at § 46.102(d). The regulations define "human subject" as "a living individual about whom an investigator . . . conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information." *Id.* at § 46.102(f).

would comprise standard diagnostic tests or treatment.<sup>49</sup> In addition to ensuring that risks to subjects are minimized, the IRB must evaluate whether those risks, whatever their magnitude, are reasonable in relation to the probable benefits to the subjects and the importance of the anticipated scientific knowledge.<sup>50</sup> Thus, the IRB must weigh potential risks and benefits to subjects who participate in the research.<sup>51</sup>

This inquiry is necessarily complex and fact-intensive. In the case of therapeutic research, where the subjects suffer from the condition under investigation, there are both potential risks and direct benefits to participation. In non-therapeutic research, however, there is no prospect of direct benefit to the participants and concerns about coercion loom large.<sup>52</sup> In such cases, the IRB evaluates whether the possible benefit to society in the form of improved scientific

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<sup>49</sup> 45 C.F.R. § 46.111(a)(1) (2003).

<sup>50</sup> *Id.* at § 46.111(a)(2). IRBs do not, as a general matter, consider the ultimate cost of an experimental therapy, though perhaps they should. After all, if the experimental product will be very expensive compared with other available, efficacious therapies and thus will not constitute an important addition to the treatment arsenal for a particular condition, perhaps the benefits of the research may not justify its risks. Because the cost of some new therapies appears justified in patients who do not respond well to cheaper alternatives, however, and because IRBs have no crystal ball to determine which new therapies will fill such a niche, this cost generally remains irrelevant to the IRB's assessment of the value of the potential scientific knowledge being sought. Compare Jean-Michel Gaspoz et al., *Cost Effectiveness of Aspirin, Clopidogrel, or Both for Secondary Prevention of Coronary Heart Disease*, 346 NEW ENG. J. MED. 1800, 1803 (2002) (concluding that the use of aspirin alone was the most cost-effective treatment for cardiac patients despite the fact that adding the more expensive drug clopidogrel increased therapeutic benefit), with Alastair J.J. Wood, *When Increased Therapeutic Benefit Comes at Increased Cost*, 346 NEW ENG. J. MED. 1819 (2002) (criticizing the study authors' recommendations, and arguing that the search for improved drug therapies should not be abandoned based on concerns about what they characterized as "unattractive" cost).

<sup>51</sup> See 45 C.F.R. § 46.111(a)(2) (2003) ("In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research [as distinguished from the risks and benefits of therapies subjects would receive even if not participating in the research]."). Not surprisingly, it is sometimes difficult for the subjects themselves to separate research-related treatments from standard therapies, especially if they are receiving both simultaneously and, therefore, difficult for prospective research subjects to weigh risk and benefit in deciding whether to participate. See *infra* notes 65-70 and accompanying text. Although the regulations only require IRBs to categorize risk for research involving children, see 45 C.F.R. § 46.403-.407 (2003), it is common practice for IRBs to categorize risk in all research protocols. In the context of research on adults, the federal regulations only define "minimal risk." *Id.* at § 46.102(i). Thus, IRBs must use their own judgment in determining what research activities constitute greater than minimal risk.

<sup>52</sup> Observers may find it difficult to believe that altruism alone motivates participants in non-therapeutic research. Investigators may find it very difficult to recruit volunteers to participate in research with no prospect of therapeutic benefit in the absence of a monetary incentive, unless the investigator seeks "volunteers" in an arguably coercive type of setting like the educational or employment context. For example, an expert panel that reviewed research protections at Johns Hopkins after Ellen Roche's death expressed concern that the University pressured employees into volunteering for research studies. See Tom Pelton, *Experts Fault Study Review at Hopkins*, BALT. SUN, Aug. 30, 2001, at A1 (adding that the outside review panel had concluded that an "adversarial relationship" existed between Hopkins and federal regulators and that the Hopkins human subjects protection system was weaker than at other research institutions).

understanding justifies the risks to individual research participants. For example, Phase I clinical trials to assess the safety and appropriate dosing levels of an investigational new drug provide no direct benefit to the study subjects but represent a necessary step in the development of potentially useful drug therapies that ultimately may benefit large numbers of patients. An IRB may conclude that such research, if appropriately designed, meets the ethical standards implicit in the regulations.

IRBs also must assess the broader scientific merit of each research proposal, a task that includes risk-benefit analysis but also considers the place of a particular research plan in the broader field of scientific inquiry. Research that lacks scientific merit is per se unethical and must not receive IRB approval. The assessment of scientific merit may prove difficult, however, even for a board of scientists and physicians.<sup>53</sup> For example, if a protocol is designed to assess the safety and efficacy of a drug that will be the tenth in its therapeutic class and the study involves significant risk of side effects, the IRB may opt against approval. Similarly, IRBs may reject placebo-controlled studies that deny participants access to available standard therapy.<sup>54</sup> In contrast, the IRB may more willingly tolerate a significant degree of risk to participants in a drug study involving a new molecular entity or other novel therapy intended to treat a serious or life-threatening condition for which available treatments are inadequate, even when the investigator provides only limited pre-clinical and clinical data about safety and effectiveness.<sup>55</sup> The regulations offer little guidance to IRBs in making these kinds of ethical assessments, yet IRBs tend to spend proportionately less time on the analysis of risk and benefit than on other matters such as informed consent and confidentiality.<sup>56</sup>

The informed consent process is designed to reduce the knowledge gap between physician and patient by mandating the communication of sufficient

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<sup>53</sup> On the contingency of these sorts of judgments, see Lars Noah, *Pigeonholing Illness: Medical Diagnosis as a Legal Construct*, 50 HASTINGS L.J. 241 (1999).

<sup>54</sup> See *infra* notes 252-260 and accompanying text.

<sup>55</sup> See Karen Antman et al., *Designing and Funding Clinical Trials of Novel Therapies*, 344 NEW ENG. J. MED. 762, 762 (2001) (observing that “[t]here are no clear criteria for determining when a procedure is optimally developed and when it is ready for randomized testing”).

<sup>56</sup> See Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J.L. & MED. 361, 384 (2002) (“IRBs may become preoccupied with reviewing the niceties of the consent form and perhaps less concerned about their separate obligation to make independent risk-benefit assessments about the research protocol, confident that potential subjects can ‘vote with their feet’ so long as the consent form contains all of the necessary information.”); see also Charles Weijer, *The Ethical Analysis of Risk*, 28 J.L. MED. & ETHICS 344, 344 (2000) (explaining that IRBs have the obligation to ensure that research subjects for both therapeutic and non-therapeutic research “are presented with the option of entering a research study only when agreeing to do so would be a reasonable choice”).

information to allow the patient to make meaningful decisions about health care.<sup>57</sup> It serves much the same purpose for potential subjects in their dealings with investigators. Informed consent represents a necessary, though insufficient, requirement for ethically appropriate research.<sup>58</sup> The regulations require that investigators obtain and document informed consent from each research subject.<sup>59</sup> The consent form must use language that the subject can comprehend.<sup>60</sup> Both sets of regulations demand essentially identical elements in the disclosure of research procedures and risks to potential participants, including a description of the procedures to be followed, identification of any procedures which are experimental, a description of any reasonably foreseeable risks or discomforts to the subject, a description of any prospective benefits to the subject or to others, a discussion of alternative procedures or courses of treatment, if any, that might be advantageous to the subject, and a statement that participation is voluntary and that the subject may discontinue participation at any time without penalty.<sup>61</sup>

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<sup>57</sup> See generally Robert Gatter, *Informed Consent Law and the Forgotten Duty of Physician Inquiry*, 31 LOY. U. CHI. L.J. 557 (2000) (analyzing the requirements of informed consent and arguing that it should require the physician to know personal information regarding the patient as a prerequisite to legally sufficient consent); Joan H. Krause, *Reconceptualizing Informed Consent in an Era of Health Care Cost Containment*, 85 IOWA L. REV. 261, 267 (1999).

<sup>58</sup> See Ezekiel J. Emanuel et al., *What Makes Clinical Research Ethical?*, 283 JAMA 2701, 2701-04 (2000) (discussing seven requirements, including informed consent, essential to the conduct of truly ethical research); see also Richard W. Garnett, *Why Informed Consent? Human Experimentation and the Ethics of Autonomy*, 36 CATH. LAW. 455, 476-77 (1996) (explaining that informed consent in research pays "comparatively little attention" to whether the experiment itself is ethical).

<sup>59</sup> 45 C.F.R. § 46.111(a)(4)-(5) (2003). If the research subject is unable to understand the research and give informed consent, the investigators must obtain consent from the individual's legally authorized representative. *Id.*

<sup>60</sup> Despite the fact that many IRBs have interpreted the "language understandable to the subject" clause in this regulation to require informed consent forms to be written at an 8th grade reading level, comprehension problems remain. An IRB might direct an investigator to redraft the following statement of risks: "You will be asked to undergo bi-weekly venipuncture during which 10 ccs of blood will be collected. The risks of venipuncture include syncope and infection, but these risks occur only sporadically." The redrafted statement might read as follows: "You will have 2 teaspoons of your blood drawn every other week from a vein. There is a small chance that you could faint during the blood draw or get an infection at the site of the needle stick." See Stanley Blenkinsop, *Whatever Happened to Plain English? The Gobbledygook Smokescreen that Baffles Research Subjects*, in VOLUNTEERS IN RESEARCH AND TESTING 89-93 (Bryony Close et al. eds., 1997) (observing that "[t]here must be some suspicions that those unable to organise a clear, effective written explanation are equally unable to organise a clear, effective research programme," and providing some egregious examples of consent form "gobbledygook" with translations); Dale E. Hammerschmidt & Moira A. Keane, *Institutional Review Board (IRB) Review Lacks Impact on the Readability of Consent Forms for Research*, 304 AM. J. MED. SCI. 348, 349-50 (1992) (concluding that the IRB review process only improved consent form readability by an average of one-tenth of a grade level); Michael K. Paasche-Orlow et al., *Readability Standards for Informed-Consent Forms as Compared with Actual Readability*, 348 NEW ENG. J. MED. 721, 723-24 (2003) (providing examples of informed consent text at a variety of reading levels, and concluding that most medical schools did not comply with their own internal readability requirements).

<sup>61</sup> 45 C.F.R. § 46.116(a) (2003). In certain cases, the regulations require additional consent information, including statements about the risk to the fetus where the research involves pregnant

Once the IRB approves the protocol and the consent form, the process of obtaining consent is left to the principal investigator or, more often, to his or her staff.<sup>62</sup> Unfortunately, the actual process of obtaining consent in research often emphasizes form over substance and thus falls short of promoting the ethical ideal of patient autonomy in making medical decisions.<sup>63</sup> Although HHS has recommended the use of ombudsmen or other third parties to monitor the consent process in unusually sensitive or risky protocols, it has imposed no specific requirements to encourage consent monitoring, and IRBs continue to lack the resources to perform this function.<sup>64</sup>

Research designed primarily to advance medical knowledge, with only a speculative possibility of some secondary benefit to the research subjects, heightens these concerns and makes meaningful informed consent essential.<sup>65</sup> Even when the IRB and the principal investigator manage to draft an easy-to-read informed consent document and provide the potential research participant with an oral explanation of the research and an opportunity to ask questions, research subjects sometimes fail to understand the distinction between the standard therapy that they would ordinarily receive for their condition and the experimental therapy.<sup>66</sup> The confusion multiplies when patients receive standard and

women, circumstances under which the subject's participation may be terminated by the investigator, additional costs to the subject, and the number of subjects involved in the study. *Id.* at § 46.116(b). The IRB may elect to approve a consent process that alters some of the elements described above in cases where the research "could not practicably be carried out without the waiver or alteration." *Id.* at § 46.116(b)(2), (d).

<sup>62</sup> The IRB has the option of appointing a "consent monitor" to oversee this process. *See id.* at § 46.109(e). IRBs rarely have the resources to exercise this authority. *See* BERG ET AL., *supra* note 47, at 260 (recommending that IRBs pay less attention to informed consent forms and "make efforts to evaluate the actual consent interaction").

<sup>63</sup> *See* BERG ET AL., *supra* note 47, at 200. According to Franz Ingelfinger, "[t]he patient, asked to sign countless releases or consents, may respond with a . . . pro forma signature. The physician, immersed in a profusion of unimportant detail, will lose sight of, and respect for the important issues. . . . For medical ethics, in short, trivialization is self-defeating." *Id.* For a detailed discussion of these points, including a critique of the practice of obtaining consent in the research context, see Richard Delgado & Helen Leskovic, *Informed Consent in Human Experimentation: Bridging the Gap Between Ethical Thought and Current Practice*, 34 UCLA L. REV. 67, 75-80 (1986).

<sup>64</sup> *See* HHS Status Report, *supra* note 8, at 12-13.

<sup>65</sup> *See* Jay Katz, *Human Experimentation and Human Rights*, 38 ST. LOUIS U. L.J. 7, 41-51 (1993) (describing a study designed to evaluate rates and mechanisms of schizophrenic relapse in patients who were withdrawn from all antipsychotic medications in which participants were informed that their condition "may improve, worsen, or remain unchanged" despite the fact that the rate of serious relapse among patients who ceased medications was 88%).

<sup>66</sup> *See* Paul S. Appelbaum et al., *False Hopes and Best Data: Consent to Research and the Therapeutic Misconception*, HASTINGS CTR. REP., Apr. 1987, at 20, 21 (explaining the difficulty that many patient/subjects experience in understanding that the design of a research study generally focuses on generating useful scientific data rather than on delivering the best therapeutic option for the individual participant); *see also* Paul S. Appelbaum, *Clarifying the Ethics of Clinical Research: A Path Toward Avoiding the Therapeutic Misconception*, 2 AM. J. BIOETHICS 22 (2002); Sarah J.L. Edwards et al., *The Ethics of Randomised Controlled Trials from the Perspectives of Patients, the Public, and*

experimental interventions simultaneously.<sup>67</sup> These problems compromise research subjects' ability to weigh the risks and benefits of participation effectively.

In addition, even in protocols that offer some real possibility of prospective benefit, informed consent seldom includes information about the likelihood that such benefit will occur for any one research subject. Moreover, consent forms rarely discuss the possibility that the experimental intervention under study may not work as well as standard therapy for a given condition,<sup>68</sup> or remind research subjects of their option not to participate based on concerns that experimental therapy entails additional and often unpredictable risks compared with standard

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*Healthcare Professionals*, 317 BRIT. MED. J. 1209, 1209 (1998) (finding that many participants in clinical trials enroll because they hope to benefit personally rather than for altruistic reasons); Katie Featherstone & Jenny L. Donovan, *Random Allocation or Allocation at Random? Patients' Perspectives of Participation in a Randomised Controlled Trial*, 317 BRIT. MED. J. 1177, 1179-80 (1998) (concluding that many trial participants found the concept of randomization confusing); Samuel Hellman & Deborah S. Hellman, *Of Mice but Not Men: Problems of the Randomized Clinical Trial*, 324 NEW ENG. J. MED. 1585, 1585-86 (1991) (explaining that medical research is designed to verify scientific hypotheses, not to treat ill patients).

<sup>67</sup> Many patients apparently fail to understand that they have agreed to participate in a research protocol rather than (or in addition to) receiving standard therapy, and many cannot adequately balance the risks and benefits of participation even after completing the informed consent process. A 1995 survey of 371 research subjects found that nearly 20% of those questioned incorrectly believed that they were not and never had been research subjects. See Laura C. McBride & Mark R. Yessian, *IRBs and Continuing Review: Regulatory Interference or Vital Safeguard?*, 16 FOOD DRUG COSM. & MED. DEV. L. DIG. 13, 15 (1999); see also George J. Annas, *Questing for Grails: Duplicity, Betrayal and Self-Deception in Postmodern Medical Research*, 12 J. CONTEMP. HEALTH L. & POL'Y 297, 319-21 (1996) (reviewing evidence of trial participants' inability to distinguish research interventions from standard therapy and the contribution of inadequate consent forms to this confusion); Franklin G. Miller & Donald L. Rosenstein, *The Therapeutic Orientation to Clinical Trials*, 348 NEW ENG. J. MED. 1383, 1384 (2003) (explaining that a variety of research practices, including referring to subjects as "patients" and advertising for trial participants who are suffering from the disease and need treatment, perpetuates the therapeutic misconception, and emphasizing that the traditional ethics of the doctor-patient relationship cannot govern the investigator-subject relationship); cf. Steven Joffe et al., *Quality of Informed Consent in Cancer Clinical Trials: A Cross-Sectional Survey*, 358 THE LANCET 1772, 1774-75 (2001) (finding that 71% of adult cancer patients enrolled in clinical trials at a cancer institute understood that they might not benefit directly from the trials, but that less than 40% understood that the trial procedures might involve additional risk or discomfort compared with standard therapies for their conditions).

<sup>68</sup> Commentators have observed that consent forms mislead when they fail to explain the degree of uncertainty of therapeutic benefit from an investigational intervention. If, for example, a protocol offers less than a 10% chance of benefit, merely explaining in the consent form that therapeutic benefit is "uncertain" may mislead some patients to overestimate their chance of benefit. See Sam Horng et al., *Descriptions of Benefits and Risks in Consent Forms for Phase I Oncology Trials*, 347 NEW ENG. J. MED. 2134 (2002) (surveying consent forms in Phase I oncology trials, and finding that, although 94% of forms communicated some uncertainty about benefit, 51% of forms "alluded to the possibility of benefit in a section other than the designated benefit section—usually in the statement of purpose—by including statements such as 'some patients have benefited from treatment with this drug' or 'this drug has shown some promise in this disease'"). The same study concluded that most consent forms did not distinguish between standard and experimental procedures and nearly all of the forms referred to the investigational drug under study as a "treatment." *Id.* at 2136, 2139.

medical interventions.<sup>69</sup> Finally, in their zeal to answer a challenging scientific question, researchers sometimes deliberately downplay or omit information about the medical uncertainty inherent in such research in order to optimize enrollment in the protocol.<sup>70</sup>

In addition to requiring meaningful informed consent, the regulations prohibit research that employs “coercive” tactics,<sup>71</sup> but IRBs sometimes struggle to determine what sorts of recruitment techniques would constitute coercion. For many years, recruitment of research subjects has involved payment for participation, although most IRBs agree that this practice poses difficult ethical problems.<sup>72</sup> Depending on how they are structured, such incentives clearly can pose a risk of coercion, particularly because low-income or uninsured individuals are more likely to enroll in a research study in order to obtain otherwise

<sup>69</sup> See Delgado & Leskovic, *supra* note 63, at 88.

<sup>70</sup> See BERG ET AL., *supra* note 47, at 287 (describing observational studies and FDA informed consent audits that found distortion or concealment of important information in the informed consent process in research, including a failure to disclose the experimental nature of the proposed research intervention 53% of the time). One physician recently described a study he conducted early in his career in which he paid healthy medical students to participate, one of whom experienced a serious adverse effect from the study intervention, despite the fact that he had described the risks involved as “nominal.” The physician discussed the factors that motivated him to perform the research, explaining that his “primary motive was . . . the desire to advance knowledge about an important physiological mechanism” but that “[a] potent secondary motive was to advance [his] career by publishing the results of the research and maintaining grant support – academic currency that buys prestige and promotion.” Norman G. Levinsky, *Nonfinancial Conflicts of Interest in Research*, 347 NEW ENG. J. MED. 759, 759 (2002).

<sup>71</sup> 45 C.F.R. § 46.116 (2003) (providing that the “investigator shall seek . . . consent only under circumstances that provide the prospective subject . . . sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence”). See also Sharona Hoffman, *Regulating Clinical Research: Informed Consent, Privacy, and IRBs*, 31 CAP. U. L. REV. 71, 85 (2003) (observing that “[g]enuine informed consent is particularly difficult to obtain when the patients . . . suffer from life-threatening diseases,” and suggesting that “those who have the most to gain or lose from receiving experimental treatment are also those who are least able to provide meaningful informed consent”).

<sup>72</sup> See Neal Dickert & Christine Grady, *What’s the Price of a Research Subject? Approaches to Payment for Research Participation*, 341 NEW ENG. J. MED. 198, 198 (1999). Payments may include non-monetary incentives as well. Recently, some protocols to test drugs in pediatric populations have offered gift certificates to toy stores in addition to cash and free study medications. See Alice Dembner, *Teddy Bears and Veiled Threats to Attract Children into Medical Experiments*, BOSTON GLOBE, Mar. 20, 2001, at C1 (describing the practice of offering gift certificates to McDonalds and Toys ‘R’ Us stores as “an ethical gray zone”). IRBs also worry about the impact of catchy but potentially misleading trial acronyms, such as BRAVO and GUSTO. See Michael Berkwitz, *Capture! Shock! Excite! Clinical Trial Acronyms and the “Branding” of Clinical Research*, 133 ANNALS INTERNAL MED. 755, 757-58 (2000) (explaining that the use of such acronyms functions like a clinical trial advertisement and may convey a misleading impression to trial participants about the studied therapy’s safety and effectiveness).

unavailable treatment and are more likely to underestimate the risks.<sup>73</sup> Federal guidelines offer little assistance in dealing with this thorny issue, and the research community so far has failed to reach a consensus about it.<sup>74</sup> Nevertheless, researchers, patient advocates, and ethicists appear to agree on some basic principles such as preferring payments that compensate for travel expenses and lost time at work, but that are not so large as to be unduly influential. Many IRBs also require pro-rated payments rather than permitting the withholding of all payment until a research participant completes all of the study interventions. Some commentators have suggested several alternative models of compensation for both patients and healthy volunteers who participate in research protocols,<sup>75</sup> but, for now, IRBs continue to debate whether financial compensation in any protocol presents an inappropriate inducement that could render consent invalid.

## 2. *Ongoing Supervision of Approved Protocols*

IRBs must revisit approved protocols at least annually, and more frequently if the degree of risk demands it, in a process called “continuing review.”<sup>76</sup> In such a review, the board examines adverse events (with particular attention to serious, unexpected events) and should ensure that the investigator has complied with informed consent requirements by obtaining consent from each subject, documenting that consent, and providing the subject with a copy of the consent document and information about whom to contact in case of problems. The IRB

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<sup>73</sup> See HHS Report, *supra* note 8, at A-2; Dickert & Grady, *supra* note 72, at 198-99; see also Barbara A. Noah, *The Participation of Underrepresented Minorities in Clinical Research*, 29 AM. J.L. & MED. 221 (2003).

<sup>74</sup> The HHS regulations do not address the issue of payment, and the OHRP and FDA guidelines on the subject leave the controversy unresolved, noting, unhelpfully, that “[t]he IRB should review both the amount of payment and the proposed method of timing of disbursement to assure that neither are coercive or present undue influence.” FDA, GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS AND CLINICAL INVESTIGATORS (1998), available at <http://www.fda.gov/oc/ohrt/irbs/toc4.html#payment> (last visited July 1, 2004).

<sup>75</sup> See Dickert & Grady, *supra* note 72, at 199-201 (discussing the relative merits of the market model, the wage-payment model, and the reimbursement model for compensating research subjects, and concluding that the wage-payment model most effectively reduces concerns about undue inducement).

<sup>76</sup> 45 C.F.R. § 46.109(e) (2003) (“An IRB shall conduct continuing review of research . . . at intervals appropriate to the degree of risk . . .”). The NIH’s web-based training course for IRB members offers the following example of a situation in which an IRB might require updated reports more frequently than annually: a Phase I clinical trial to study increasingly higher doses of a new chemotherapeutic drug will take a year to complete and will enroll twenty subjects—five sets of four—with each set receiving increasing doses. Under these circumstances, the IRB might require the investigator to report evidence of toxicity or other adverse events after each dosing set. NIH, COMPUTER-BASED TRAINING COURSE FOR NIH IRB MEMBERS (1999), (on file with the Journal of Health Care Law & Policy). Information about the NIH’s web-based training course can be accessed online at <http://ohsr.od.nih.gov/cbt/cbt.html> (last visited July 1, 2004). See generally Sharona Hoffman, *Continued Concern: Human Subject Protection, the Institutional Review Board, and Continuing Review*, 68 TENN. L. REV. 725 (2001) (providing an overview and critique of the continuing review process, and recommending avenues for reform).

also must inquire whether there have been any deviations from the approved protocol, such as enrolling more than the approved number of subjects or changing study procedures.<sup>77</sup> If an IRB discovers that clinical investigators are not complying with the board's requirements, or have deviated from an approved protocol, it has the authority to suspend or terminate approval of the project.<sup>78</sup> Unfortunately, continuing review remains a "paper-based" activity at most IRBs, which generally lack the resources to visit study sites or to interview principal investigators or research subjects. Instead, IRBs usually rely on self-reporting from researchers as the basis for continuing review.<sup>79</sup>

In addition, some protocols include a provision requiring ongoing supervision of approved research (between continuing reviews by the IRB) by an oversight committee such as a data safety monitoring board (DSMB).<sup>80</sup> The IRB may rely on the promised additional supervision of the oversight committee when making the initial determination of whether the risks to potential human subjects are appropriate in relation to the benefits of participation in the research. If, however, the oversight committee fails to meet, or fails to submit reports to the IRB, it thwarts the purpose for including such a provision in the protocol. The NIH requires that all NIH-funded trials have an appropriate oversight system, including DSMBs for certain types of clinical trials. The FDA and NIH also have announced that they will require sponsors of all gene therapy protocols to submit their monitoring plans in advance for review.<sup>81</sup> These requirements apply only to a small proportion of clinical research, however, and HHS continues to urge more careful supervision of research in progress.<sup>82</sup>

The minimum annual continuing review represents only a part of the IRB's supervisory responsibilities. Boards also must review reports of adverse events associated with approved research in order to determine whether any immediate action is needed. Each IRB must provide assurances to federal funding agencies that it has written internal procedures detailing the circumstances under which

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<sup>77</sup> Such protocol changes generally require full board approval before the investigator implements them, "except when necessary to eliminate apparent immediate hazards to the subject." 45 C.F.R. § 46.103(b)(4)(iii) (2003).

<sup>78</sup> *Id.* at § 46.113. If the board suspends or terminates an approved protocol under these circumstances, it must report its actions immediately to the investigator, appropriate institution officials, and to the relevant federal department or agency (if federal funding is involved). *Id.* at § 46.103(b)(5). The FDA's regulations require a similar report. 21 C.F.R. § 56.113 (2003).

<sup>79</sup> See HHS Report, *supra* note 8, at 6-7.

<sup>80</sup> See Jay Herson, *Data Monitoring Boards in the Pharmaceutical Industry*, 12 STAT. MED. 555 (1993) (describing the duties of these boards in different contexts such as NIH clinical trials and industry-sponsored trials); Michael A. Morse et al., *Monitoring and Ensuring Safety During Clinical Research*, 285 JAMA 1201, 1202 (2001) (describing the role of these boards in analyzing data from trials in progress).

<sup>81</sup> See HHS Status Report, *supra* note 8, at 13.

<sup>82</sup> See HHS Status Report, *supra* note 8, at 12-13.

investigators must report unanticipated risks or problems with the research or deviations from the approved protocol prior to the continuing review.<sup>83</sup> Whenever the board receives reports of adverse events, it must determine whether a particular event (or an accumulation of adverse events) indicates a change in the risk-benefit calculus that requires some type of corrective action.<sup>84</sup>

The recent increase in the pace of clinical research has left IRBs inundated with adverse event reports. OHRP has noted a tripling of research-related injury reports between 1997 and 2000, which it attributes in part to an increased awareness of federal reporting regulations among researchers.<sup>85</sup> Not surprisingly, boards find it difficult to devote serious attention to reviewing and addressing these reports.<sup>86</sup> The effectiveness of the adverse event monitoring system for human subjects depends heavily on voluntary compliance with IRB and federal regulatory reporting guidelines,<sup>87</sup> but recent reports suggest that many researchers routinely fail to report injuries and deaths among their study patients.<sup>88</sup> Increasingly, large,

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<sup>83</sup> 45 C.F.R. § 46.103(b)(5) (2003) (requiring that boards create “written procedures for ensuring prompt reporting to the IRB . . . of any unanticipated problems involving risks to subjects or . . . any serious or continuing noncompliance with . . . the requirements or determinations of the IRB”). In these circumstances, IRBs have the authority to halt research. *Id.* at § 46.113.

<sup>84</sup> IRB action in response to serious adverse events might include requiring additional warnings in the informed consent form (and obtaining new consent from subjects enrolled in the trial), requiring changes to the protocol to guard against future adverse events if such changes will prevent or reduce the incidence of such events, or suspending or terminating the protocol altogether.

<sup>85</sup> Pelton, *supra* note 7, at A1.

<sup>86</sup> See HHS Report, *supra* note 8, at 7 (describing one IRB that received 200 adverse event reports per month).

<sup>87</sup> See Pelton, *supra* note 7, at A1 (explaining the difficulties of implementing the federal law, which requires only reports of regulatory violations and of unexpected adverse events that are probably connected with the experimental treatment); cf. Barbara A. Noah, *Adverse Drug Reactions: Harnessing Experiential Data to Promote Patient Welfare*, 49 CATH. U. L. REV. 449, 469-70 (2000) (describing the curious system of “mandatory” manufacturer reporting of adverse events associated with approved drug products, and observing that, because the system relies on voluntary reports of adverse events from physicians to manufacturers, the system is only as effective as the degree of voluntary physician participation permits).

<sup>88</sup> One study examined reporting practices in NIH-sponsored research. Noting that the NIH has an estimated 7 million participants in current clinical trials, the study of NIH-sponsored researchers uncovered only 878 reports of injuries and deaths in research over a ten year period and concluded that this reporting rate was “absurdly low” because the normal death rate in a population of 7 million is 5000 deaths, “each of which should have triggered a report about whether the death was related to a drug under investigation.” See Vergano, *supra* note 2, at D12 (adding that the 878 reports triggered only 41 investigations by OHRP). Another study concluded that OHRP’s predecessor received a total of only 386 reports of unexpected adverse events from academic research institutions during the 1990s, 158 of which were from a single university that now describes itself as “overzealous.” See Kranish, *supra* note 25, at A1 (reporting that, in contrast, the pharmaceutical industry regularly provides adverse events to the FDA: approximately 241,000 reports between 1987 and 2001); see also John P.A. Ioannidis & Joseph Lau, *Completeness of Safety Reporting in Randomized Trials*, 285 JAMA 437, 440-41 (2001) (finding deficiencies in both the quality and quantity of adverse event reporting in RCTs, and concluding that adverse event reports frequently fail to define the severity of the event adequately). Finally, just after Jesse Gelsinger’s death, the NIH sent a reminder notice to all gene therapy

multi-center trials place even greater stress on the adverse event reporting system, which was initially developed when most research was performed at single sites.<sup>89</sup> The problems inherent in the current adverse event reporting scheme have become so alarming that some observers have commented that research animals often receive better protection than human guinea pigs.<sup>90</sup>

Both the FDA and NIH have issued guidelines dealing with adverse event reporting in the clinical research setting,<sup>91</sup> though some of the NIH guidelines address only gene therapy research.<sup>92</sup> The FDA standards for expedited reporting call for the immediate notification about serious, unexpected adverse drug reactions in clinical trials.<sup>93</sup> The NIH recently finalized a new adverse event reporting guideline for gene therapy research protocols that loosens its prior requirement that all serious adverse events be reported immediately, whether apparently related to the experimental therapy or to the patient's underlying

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investigators that they were required to submit reports of adverse events and deaths in gene therapy protocols, after which it received an astounding 652 new adverse event reports, including seven prior deaths that had gone unreported. See Washburn, *supra* note 27, at W16; see also Deborah Nelson & Rick Weiss, *Earlier Gene Test Deaths Not Reported: NIH Was Unaware of "Adverse Events,"* WASH. POST, Jan. 31, 2000, at A1.

<sup>89</sup> See McWilliams et al., *supra* note 47, at 363-64 (describing the growth of multicenter studies since the early 1980s as "dramatic"); Morse et al., *supra* note 80, at 1202 (outlining the problems with research oversight and adverse event reporting, and making recommendations for reforms).

<sup>90</sup> See Kranish, *supra* note 25, at A1 (explaining that regulations require private researchers to report adverse events in research involving cats and dogs, but not necessarily events involving human subjects); see also R. Alta Charo, *Human Subjects Have It Worse Than Guinea Pigs*, CHRON. HIGHER EDUC., June 25, 1999, at A64.

<sup>91</sup> FDA, CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING (1995), available at <http://www.fda.gov/cder/guidance/iche2a.pdf> (last visited July 1, 2004) [hereinafter "FDA Reporting Guideline"]; see also 21 C.F.R. § 312.32 (c)(1) (2003) (requiring sponsors of drug studies using investigational new drugs to notify FDA of "[a]ny adverse experience associated with the use of the drug that is both serious and unexpected" and "[a]ny finding from tests in laboratory animals that suggests a significant risk for human subjects including . . . teratogenicity or carcinogenicity" within 15 calendar days of the sponsor's initial receipt of the information).

<sup>92</sup> See NIH, GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES (2002), available at <http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html> (last modified July 1, 2002). The guidelines apply to all NIH-funded research involving recombinant DNA processes and to all non-NIH-funded research involving recombinant DNA conducted at institutions receiving NIH funding for projects that involve these gene therapy techniques.

<sup>93</sup> See FDA Reporting Guideline, *supra* note 91, at 4-5 (explaining that a serious adverse event is "any untoward medical occurrence that at any dose results in death; is life threatening; . . . requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity or; is a congenital anomaly/birth defect"). The reporting standards also require investigators to make a causality assessment to determine whether the serious, unexpected adverse event is related to the study product before making an expedited report to the agency. The guideline states that "[a]ll cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the [study drug]" should be reported on an expedited basis. *Id.* at 6-7.

disease.<sup>94</sup> The guideline requires public reporting of all gene therapy adverse events but requires immediate reporting only of adverse events that are both serious and related to the experimental therapy.<sup>95</sup>

Theoretically, these more limited reporting requirements will permit both NIH and the FDA to subject this category of serious, unexpected, study-related events to more careful scrutiny.<sup>96</sup> The new NIH guideline may work more efficiently with existing FDA adverse event reporting requirements, but patient advocates are concerned that the proposed changes leave researchers with even more room for error in deciding whether particular adverse events require immediate reporting.<sup>97</sup> All of these recent developments in turn necessitate appropriate changes in IRB operations in order to achieve meaningful and efficient implementation.

### B. *Changes in the Climate of Biomedical Research*

A variety of recent developments in clinical research may contribute to the likelihood of regulatory violations or errors in supervisory judgments by IRBs. Although research administrators have acknowledged problems in the clinical research environment, not all of the problematic aspects of academic medical research receive the same degree of attention.<sup>98</sup> As the pace of medical research increases, many IRBs are staggering under the weight of their oversight responsibilities. One recent survey found that requests for initial protocol reviews increased 42% between 1993 and 1998 and that some IRBs supervise up to 2,000

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<sup>94</sup> 66 Fed. Reg. 57,970 (2001) (final notice of actions under guidelines to “[h]armonize NIH requirements for expedited reporting of serious adverse events in gene transfer trials with those of FDA”).

<sup>95</sup> *Id.* (stating that “[e]xpeditied reporting will now be required for those serious adverse events that are unexpected and associated with the use of the gene transfer product (i.e., there is a reasonable possibility that the experience may have been caused by the gene transfer product)”).

<sup>96</sup> See Rick Weiss, *Gene Research Rule Proposed*, WASH. POST, Dec. 13, 2000, at A2.

<sup>97</sup> See *id.* (reporting that patient advocates worry that researchers will make biased decisions about whether the serious adverse events are related to the experimental therapy); see also Morse et al., *supra* note 80, at 1203 (describing the confusion IRBs and investigators experience when attempting to determine which adverse events must be reported, by whom, and to whom); Jeffrey Brainard, *NIH Proposes Shift in Rules on Reporting Deaths of Gene-Therapy Patients*, CHRON. HIGHER EDUC., Jan. 5, 2001, at 33, 35 (reporting that critics of the new rule recommend that the RAC analyze all available adverse event information where the “overwhelming concern is the health and safety of the volunteers”).

<sup>98</sup> See Eric G. Campbell et al., *Status of Clinical Research in Academic Health Centers*, 286 JAMA 800, 804-05 (2001) (concluding that clinical research leadership perceived the following as the primary contributors to declining quality in the clinical research enterprise: pressure on clinical faculty to see patients, insufficient clinical revenues, difficulty in recruiting trained researchers, lack of external research support, competition from contract research organizations, problems with the IRB process, and problems with finding research participants).

ongoing research plans.<sup>99</sup> The burgeoning load of protocols requiring initial review and continuing supervision, combined with lack of adequate institutional support for IRBs,<sup>100</sup> can create a situation where an overworked IRB may be forced to do only the bare minimum required by the regulations.<sup>101</sup> Despite governmental recommendations that institutions supply their IRBs with adequate staff, funding, space, and equipment,<sup>102</sup> many boards continue to muddle along with insufficient support.<sup>103</sup>

Frequently, IRB members also lack the necessary training and expertise in the regulatory requirements, ethics, and relevant scientific principles to perform their duties optimally.<sup>104</sup> One recent study of IRB practices concluded that a quarter of the boards provide no training to their new members, while the remaining boards require only minimal training – an average of four hours for each new member, along with “a stack of material to read.”<sup>105</sup> Moreover, as medical research becomes more complex and specialized, even larger IRBs at major medical centers may lack expertise in particular scientific specialties such as gene therapy.<sup>106</sup>

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<sup>99</sup> HHS Report, *supra* note 8, at 5-6 (adding that IRB budgets and staffing have failed to keep pace with the expanding workload); *see also* Donald F. Phillips, *Institutional Review Boards Under Stress: Will They Explode or Change?*, 276 JAMA 1623, 1624 (1996) (explaining that his IRB reviews between 40 and 80 new protocols at its monthly meetings, which last up to six hours). The University of Florida's 20-member Health Center IRB is no exception: it meets twice monthly for up to six hours and supervises 2½ times as much sponsored research as it did ten years ago. In 2000, this IRB reviewed 331 new protocols and conducted 816 continuing reviews. In addition, it managed 211 new expedited reviews of protocols not requiring full board consideration. *See* UNIV. OF FLA., INSTITUTIONAL REVIEW BOARD (IRB-01), ANNUAL REPORT (2000) (report on file with the Journal of Health Care Law & Policy).

<sup>100</sup> *See* Okie, *supra* note 1, at A10 (reporting that most government agencies allocate only 1 or 2 percent of their research budget to research oversight and that the biggest sponsor of clinical research (NIH) allocates less than 0.05 percent of its research budget to oversee trials involving human subjects).

<sup>101</sup> HHS Report, *supra* note 8, at 6 (noting that, at the IRB sites visited, meetings lasted an average of 2½ hours, and included an average of 18 new protocols, 9 expedited reviews, 43 amendments, and 21 adverse event reports).

<sup>102</sup> HHS Status Report, *supra* note 8, at 15 (discussing the importance of reinforcing “to institutions and investigators that a well-supported IRB is a necessary cost of doing business”).

<sup>103</sup> It is also important to recognize that IRB activities comprise only a small proportion of most board members' professional obligations. Many IRB members have full-time duties that include teaching, clinical services, and their own research, and they must juggle IRB-related responsibilities with all of these other tasks.

<sup>104</sup> *See* Hoffman, *supra* note 76, at 736-37.

<sup>105</sup> *See* HHS Report, *supra* note 8, at 8.

<sup>106</sup> Recognizing that IRBs lack critical expertise to review certain types of highly complex medical research, the NIH recently issued guidelines requiring that all research involving recombinant DNA that receives NIH funding be approved by an Institutional Biosafety Committee with relevant expertise. Guidelines for Research Involving Recombinant DNA Molecules, 64 Fed. Reg. 25361 (May 11, 1999); *see also* Mark Barnes & Patrick Florencio, *IRBs Tend to Grow Short of Needed Skills*, NAT'L L.J. Sept. 4, 2000, at B9 (“[I]nstitutions that are the locations of cutting-edge biotechnology research often do not have staff members with the professional expertise to scrutinize these research proposals . . . . For instance, an IRB composed primarily of surgeons, pathologists and psychiatrists these days may well be asked to review complicated cutting-edge gene therapy protocols for cardiac or pulmonary illnesses.”).

Despite recommendations from government reports calling for significant improvements in funding and training, none of the relevant federal agencies has imposed educational requirements for investigators or IRB members.<sup>107</sup>

IRBs face various pressures that can compromise their effectiveness. For example, PIs may demand quick approvals or renewals of protocols in order to maintain a steady flow of research funds because many public and private financial sponsors of biomedical research condition the transfer of grant funds to research institutions on IRB review and approval. To make matters worse, because academic medical centers that receive large research grants enjoy enhanced reputations in the scientific and academic communities, an IRB may feel pressure to approve research in order to secure funding and the academic prestige that accompanies it.<sup>108</sup>

Most IRBs are comprised primarily of physicians and other health professionals employed at the research institution.<sup>109</sup> IRBs have an obligation to subject every protocol to the same level of scrutiny, whether the principal investigator is a stranger or a close colleague, but complete evenhandedness is probably unrealistic. Although board members must recuse themselves from voting on protocols in which they are listed as investigators,<sup>110</sup> IRB members frequently review their colleagues' protocols and, understandably, may find it difficult to avoid bias in favor of approval.<sup>111</sup> As one pair of commentators has observed, "there are very few provisions in the regulations that protect against bodies that might be sloppy, venal, or subservient to the institution. "Put another way, the quality of an IRB's work depends to an inordinate degree on the conscience and commitment of its volunteer members."<sup>112</sup>

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<sup>107</sup> See HHS Status Report, *supra* note 8, at 14 (adding, however, that NIH intramural researchers must complete training, and recommending that NIH extend the training requirement to its extramural researchers); see also INST. OF MED., PRESERVING PUBLIC TRUST: ACCREDITATION AND HUMAN RESEARCH PARTICIPANT PROTECTION PROGRAMS 2-4 (2001), available at [http://www.nap.edu/html/public\\_trust/reportbrief.pdf](http://www.nap.edu/html/public_trust/reportbrief.pdf) (last visited July 1, 2004) (describing a model accreditation process for human research participant protection programs).

<sup>108</sup> See Janet Fleetwood, *Conflicts of Interest in Clinical Research: Advocating for Patient-Subjects*, 8 WIDENER L. SYMP. J. 105, 111 (2001).

<sup>109</sup> The regulations describing the composition of the IRB require "at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution." 45 C.F.R. § 46.107(d) (2003). This "community member" theoretically will serve as a bulwark against decisions that place institutional interests above research subject interests.

<sup>110</sup> See *id.* § 46.107(e).

<sup>111</sup> See Fleetwood, *supra* note 108, at 111; see also Katz, *supra* note 65 at 41 (arguing that, "particularly in the murky area of informed consent, it is unlikely that members of IRBs will hold investigators to a standard of disclosure and consent that would protect the subjects of research if doing so would place impediments on the conduct of research and, in turn, affect the well being of their colleagues").

<sup>112</sup> See Edgar & Rothman, *supra* note 30, at 493.

The federal regulations forbid institutional reversals of IRB decisions to reject a protocol,<sup>113</sup> but they do little to prevent lobbying of board members. Junior faculty at academic institutions who serve on the IRB may fear reprisals in the form of delayed promotion or tenure, or subtler forms of “shunning,” if they fail to support their senior colleagues’ research.<sup>114</sup> Some IRB members have quit their boards in response to internal pressure to approve and continue ethically questionable studies that bring in significant research funding.<sup>115</sup> Although HHS has recommended that IRBs include more non-institutional members and that institutions protect their IRBs from inappropriate pressure by ensuring that boards remain segregated in the institutional hierarchy from divisions responsible for securing research funds, there has been scant progress in the past few years toward meeting these goals.<sup>116</sup> The FDA recently floated a proposal designed in part to prevent researchers whose protocols receive negative reviews from shopping around for a friendlier forum, but these measures probably will do little to reduce the pressure on the IRB conducting the initial review.<sup>117</sup>

Financial conflicts of interest are disturbingly prevalent in biomedical research.<sup>118</sup> Every year, more dollars flow into the clinical trials business. The pharmaceutical industry spends approximately \$9 billion annually on research, while the NIH and other government programs provide \$5 billion yearly in

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<sup>113</sup> Once an IRB has approved a research protocol, the parent institution has the authority to subject the protocol to additional review, if desired, but the institution may not approve research that already has been rejected by the IRB. 45 C.F.R. § 46.112 (2003).

<sup>114</sup> See Edgar & Rothman, *supra* note 30, at 492 (observing that “powerful people within an institution have a myriad of largely untraceable ways for punishing an obstructionist IRB member: from withholding or delaying promotion to blocking his or her access to other grants—a fact that no IRB member can fail to recognize”); see also Bartolo, *Tales of Informed Consent: Four Years on an Institutional Review Board*, 2 HEALTH MATRIX 193 (1992); Dale Keiger & Sue De Pasquale, *Trials and Tribulation*, JOHNS HOPKINS MAG., Feb. 2002, at 15 (describing IRB and institutional politics at Hopkins).

<sup>115</sup> See David Heath & Duff Wilson, *System’s Serious Flaws Have Led Many to Call for Regulatory Reform*, SEATTLE TIMES, Mar. 15, 2001, at A11 (quoting one of the ten members of the IRB at the University of Illinois at Chicago who quit: “They thought we were overly scrupulous, nitpicking obstructionists who were spoiling the research-enterprise system”).

<sup>116</sup> See HHS Status Report, *supra* note 8, at 15.

<sup>117</sup> See 67 Fed. Reg. 10115 (2002) (proposing an amendment to the FDA’s regulations that would require sponsors and investigators to report prior IRB reviews of a protocol to “ensure that sponsors and clinical investigators who submit protocols to more than one IRB will not be able to ignore an unfavorable IRB review decision and that IRBs reviewing a protocol will be aware of what other IRBs . . . have concluded”); HHS Report, *supra* note 8, at 14 (explaining that the OIG had “heard of a few situations where sponsors and/or research investigators who were unhappy with one IRB’s reviews switched to another without the new IRB being aware of the other’s prior involvement,” and recommending mandatory disclosure of prior IRB reviews).

<sup>118</sup> See Justin E. Bekelman et al., *Scope and Impact of Financial Conflicts of Interest in Biomedical Research*, 289 JAMA 454, 463 (2003) (reviewing over 1600 published studies, and finding that one-fourth of clinical researchers had industry affiliations and about two-thirds of academic institutions held equity in companies that sponsored research at the same institutions).

research funding.<sup>119</sup> Financial arrangements between medical technology companies and academic researchers, community physicians, and private contract research organizations (CROs)<sup>120</sup> have captured the attention of regulatory agencies and the academic and medical communities.<sup>121</sup> These increasingly common collaborative research agreements between private corporations and universities, which can include stock options, profitable research subject enrollment bonuses, and generous consulting fees,<sup>122</sup> have the potential to generate immense profits for both types of entities.<sup>123</sup> At the same time, however, such

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<sup>119</sup> See Pound, *supra* note 45, at A1 (reporting one lawyer's characterization of the research system as "Nasdaq medicine"); cf. Thomas Bodenheimer, *Uneasy Alliance—Clinical Investigators and the Pharmaceutical Industry*, 342 NEW ENG. J. MED. 1539, 1539 (2000) (estimating that pharmaceutical and biotechnology companies provide 70% of funding for clinical trials); Washburn, *supra* note 27, at W16 (citing a source that suggests that private industry funds 80% of clinical trials).

<sup>120</sup> CROs are for-profit research centers that conduct clinical trials for pharmaceutical and biotechnology companies. The emergence of CROs has created a shift in private research funding away from academic medical centers. Whereas academic medical centers received 80% of industry funding for clinical trials in the early 1990s, they received only 40% of this funding by 1998 as CROs took over much of the clinical trials business. See Bodenheimer, *supra* note 119, at 1540.

<sup>121</sup> See Marcia Angell, *Is Academic Medicine for Sale?*, 342 NEW ENG. J. MED. 1516 (2000); Karen A. Jordan, *Financial Conflicts of Interest in Human Subjects Research: Proposals for a More Effective Regulatory Scheme*, 60 WASH. & LEE L. REV. 15, 35 (2003); Frances H. Miller, *Trusting Doctors: Tricky Business When It Comes to Clinical Research*, 81 B.U. L. REV. 423, 425-27 (2001) (describing the erosion of trust between physician and patient when the physician plays the dual role of clinician and researcher); David S. Shimm & Roy G. Spece, *Conflict of Interest and Informed Consent in Industry-Sponsored Clinical Trials*, 12 J. LEGAL MED. 477 (1991); Rick Weiss & Deborah Nelson, *Gene Therapy's Troubling Crossroads*, WASH. POST, Dec. 31, 1999, at A3; *Harvard Keeps Strict Rules on Outside Research Work*, N.Y. TIMES, May 27, 2000, at A9 (describing decision by the Harvard Medical School to retain strict conflict-of-interest rules that prevent their researchers from earning significant additional income via outside work); see also Goldie Blumenstyk & David L. Wheeler, *Academic Medical Centers Race to Compete in the \$3.2-Billion Drug-Testing Market*, CHRON. HIGHER EDUC., Mar. 20, 1998, at A39 (describing university efforts to attract drug industry funding to conduct clinical trials at their institutions). Commentators correctly have pointed out that a ban on industry funding remains impractical in the absence of equivalent funding from other sources. See, e.g., Mark Friedberg et al., *Evaluation of Conflict of Interest in Economic Analyses of New Drugs Used in Oncology*, 282 JAMA 1453, 1456 (1999). Cutting industry funding without some sort of practical substitute would undoubtedly have a negative impact on the progress of pharmaceutical research.

<sup>122</sup> See Washburn, *supra* note 27, at W16 (describing examples of academic-industry ties, such as the Massachusetts Institute of Technology's five-year, \$15 million agreement with Merck & Co. that grants the corporation patent rights for all jointly discovered products).

<sup>123</sup> In 1980, Congress enacted the Bayh-Dole Act which permits universities to patent inventions and products arising out of federally-funded research. Pub. L. No. 96-517, § 6(a), 94 Stat. 3019 (1980) (codified as amended at 35 U.S.C. §§ 200-212 (2000)). See generally Rebecca S. Eisenberg, *Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research*, 82 VA. L. REV. 1663 (1996) (discussing the affect of federal legislation granting patent rights on federally-sponsored research efforts). From that point forward, industry-academic collaborations have become increasingly common. See Washburn, *supra* note 27, at W16.

arrangements complicate the process of IRB review and supervision because they increase the potential for inappropriate research conduct.<sup>124</sup>

IRBs can serve as a bulwark against the potentially negative consequences of academic-industry partnerships. By overseeing research protocols designed to test the safety and effectiveness of investigational drugs, medical devices, and biotechnology products, IRBs enable sponsors to collect the data necessary for FDA review of potentially profitable products. Despite the fact that most clinical research receives extramural funding support, the IRB must resist a pattern of presumptive cooperation with investigators who rely on board approval to facilitate the receipt of research grants for the institution.<sup>125</sup>

Unfortunately, financial connections between researchers and sponsors may cause deliberate or unintentional distortion of the risks and benefits of research in ways that IRBs may find difficult to detect and correct. When investigators receive substantial grant money from study sponsors in the form of consulting fees, subject enrollment fees, corporate equity interests, or honoraria, these payments can increase the risk of subjecting the research participants to avoidable harm.<sup>126</sup> The IRB ordinarily relies on the promise of generating sound scientific data as part of the justification for placing human subjects at risk in research. Financial connections between industry and clinical investigators can make a mockery of these assumptions or at least can add complexity to the risk-benefit calculus.<sup>127</sup> Even if the conflict of interest does not cause direct harm to research subjects, the very fact that individuals are enrolled in a clinical trial (with its additional

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<sup>124</sup> See HHS Report, *supra* note 8, at 7 (explaining how these arrangements threaten the independence of IRBs).

<sup>125</sup> See David M. Cocchetto, *Practical Considerations in Direct Interactions Between Sponsors and Institutional Review Boards*, 49 FOOD & DRUG L.J. 77 (1994) (urging IRBs to reject inappropriate financial relationships between investigators and sponsors in order to protect the primary interests of the research subjects). Independent, for-profit IRBs present another wrinkle in the financial conflict of interest debate. These IRBs review new protocols and supervise ongoing, approved research in exchange for a hefty fee. For more about "commercial" IRBs, see Lemmens & Freedman, *supra* note 40, at 547-49.

<sup>126</sup> See, e.g., Jesse A. Goldner, *Dealing with Conflicts of Interest in Biomedical Research: IRB Oversight as the Next Best Solution to the Abolitionist Approach*, 28 J.L. MED. & ETHICS 379, 379 (2000) (describing a research protocol in which the PI received an enrollment fee of \$1,610 per subject, which apparently created an incentive to enroll subjects in the protocol who should have been excluded due to co-existing health problems); see also *id.* at 382-85 (describing a variety of common financial conflicts of interest that may interfere with the researcher's and IRB's ability to promote the best interests of subjects); Paul E. Kalb & Kristin Graham Koehler, *Legal Issues in Scientific Research*, 287 JAMA 85 (2002); Miller, *supra* note 121, at 433-35 (describing a similar conflict of interest in research conducted by a Boston cardiologist with a substantial financial interest in a company that he co-founded and whose products he was testing in clinical trials).

<sup>127</sup> See HHS Status Report, *supra* note 8, at 15 (recommending that equity owners be prohibited from taking part in the IRB review process because "[s]uch a practice . . . establishes a situation that can undermine a perception of impartiality").

attendant risks compared to standard treatment) may be ethically objectionable if the study design lacks scientific merit.

IRBs may find it difficult, however, to persuade investigators to strike an appropriate balance between the medical needs of their subjects and the demands of the corporate sponsor whose product they are testing.<sup>128</sup> Simple disclosure of financial relationships in consent forms, for example, may not adequately address more complex issues such as the effects of sponsor-driven protocol design on risks to subjects. When an IRB approves a protocol that fails to disclose financial conflicts of interest or permits a funding entity's financial stake in the outcome of the research to distort the design or conduct of a clinical trial, the IRB fails in its primary obligations to research subjects.

These concerns about biases and conflicts are not merely speculative. Recent studies have documented a relationship between industry sponsorship and favorable outcomes. Although it is difficult to prove bias in any particular study, these analyses suggest that industry sponsorship of research influences conclusions.<sup>129</sup> The authors of one such review recommend disclosure in published work of all financial relationships so that medical professionals can more effectively evaluate the significance of the research findings,<sup>130</sup> but disclosure alone may prove inadequate in tempering the bias towards favorable

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<sup>128</sup> Obviously, the welfare of the subject deserves priority. The question then becomes whether any financial ties between researcher and company should preclude human subjects research on the company's products, or whether it is possible to obtain sufficient "transparency" in the relationships between researcher and company through disclosure requirements to protect subjects' interests. See Robert P. Kelch, *Maintaining the Public Trust in Clinical Research*, 346 NEW ENG. J. MED. 285 (2002).

<sup>129</sup> See, e.g., Richard A. Davidson, *Source of Funding and Outcome of Clinical Trials*, 1 J. GEN. INTERNAL MED. 155, 156-57 (1986) (concluding that research comparing new therapies to traditional therapies was more likely to find the new therapy superior if funded by the new therapy's manufacturer); Friedberg et al., *supra* note 121, at 1453 (concluding that studies sponsored by pharmaceutical companies resulted in unfavorable conclusions only 5% of the time, compared with non-profit-sponsored studies which reached unfavorable cost-effectiveness conclusions 38% of the time); Henry Thomas Stelfox et al., *Conflict of Interest in the Debate Over Calcium-Channel Antagonists*, 338 NEW ENG. J. MED. 101, 101 (1998) (concluding that, in studies examining the controversial question of the safety of calcium-channel blockers (CCBs) in treating cardiovascular disease, 96% of authors who supported the use of CCBs had financial ties with CCB manufacturers, compared with 60% of those who reached "neutral" conclusions about CCB safety and 37% who reached unfavorable safety conclusions); *id.* at 104 (adding that the authors of the studies disclosed their potential conflicts of interest in only 2 out of the 70 articles analyzed). It is interesting to speculate about how this apparent bias operates. Do industry sponsors select researchers for receipt of funding based on the researchers' having previously expressed positions on an issue of controversy that are consistent with the sponsor's point of view? Or does the mere fact of the industry sponsorship somehow subtly influence the researcher's decisions about study design or interpretation of results? See Friedberg et al., *supra* note 121, at 1456 (speculating about mechanisms of influence including bias towards publication of positive results, weeding out and abandoning unpromising studies early in the research process, and sponsor influence on study design).

<sup>130</sup> See Stelfox et al., *supra* note 129, at 104-05.

conclusions.<sup>131</sup> Industry also may seek to suppress publication of unfavorable sponsored research results or to “sanitize” data in a way that exaggerates the perceived success of the studied intervention.<sup>132</sup> The different manifestations of sponsorship bias may confound IRB attempts to assess accurately the scientific merit of proposed research and its risk-benefit ratio. Although IRBs generally have information about sources of sponsorship at the time of initial protocol review, it is difficult for boards to predict which industry-funded protocols may pose problems. IRBs must rely to some degree on the researcher’s assertion that the research plan is designed to generate unbiased data while at the same time protecting the interests of the subjects.

The federal regulations do little to insulate the integrity of the initial IRB review from internal or external pressures. Although the FDA and HHS regulations do contain provisions that address financial conflicts of interest, these rules focus primarily on disclosure of conflicts to government agencies rather than to IRBs and research subjects. The HHS regulations require investigators receiving funding under the Public Health Service Act (such as NIH grants) to disclose “significant financial conflicts of interest.”<sup>133</sup> FDA regulations require that sponsors disclose to the agency their investigators’ financial interests in

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<sup>131</sup> Kay Dickersin, *The Existence of Publication Bias and Risk Factors for Its Occurrence*, 263 JAMA 1385, 1386-88 (1990) (explaining that researchers are more likely to submit positive research results for publication); Monika K. Krzyzanowska et al., *Factors Associated with Failure to Publish Large Randomized Trials Presented at an Oncology Meeting*, 290 JAMA 495, 500 (2003) (concluding that bias against publishing nonsignificant study results exists even for large randomized trials and that “lack of publication of some studies, especially those with nonsignificant results, can lead to overestimation of treatment effects”); Lars Noah, *Sanctifying Scientific Peer Review: Publication as a Proxy for Regulatory Decisionmaking*, 59 U. PITT. L. REV. 677, 705-09 (1998); cf. Carin M. Olson et al., *Publication Bias in Editorial Decision Making*, 287 JAMA 2825 (2002) (concluding that, although authors with positive results are more likely to submit them for publication, journals were not significantly more likely to publish positive findings compared with negative or neutral findings).

<sup>132</sup> See Drummond Rennie, Editorial, *Thyroid Storm*, 277 JAMA 1238 (1997) (lambasting the pharmaceutical industry for its attempts to control publication of research results); see also David Blumenthal et al., *Withholding Research Results in Academic Life Sciences: Evidence from a National Survey of Faculty*, 277 JAMA 1224, 1226 (1997); James O. Kahn et al., *Evaluation of HIV-1 Immunogen, an Immunologic Modifier. Administered to Patients Infected with HIV Having 300 to 549 x 10<sup>6</sup>/L CD4 Cell Counts*, 284 JAMA 2193 (2000) (reporting unfavorable results from an industry-sponsored trial of an AIDS drug over the sponsor’s objections); David Moher et al., *The CONSORT Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Randomized Trials*, 285 JAMA 1987 (2001) (providing advice to medical study authors on how to avoid pitfalls in trial reporting); David Brown, *Scientists Report Bid to Block Publication of an AIDS Study*, WASH. POST, Nov. 1, 2000, at A10.

<sup>133</sup> 42 C.F.R. § 50.601-.605 (2003); see also Jeffrey Brainard, *U.S. Offers Guidelines on Researchers’ Conflicts of Interest*, CHRON. HIGHER EDUC., Feb. 16, 2001, at A33 (describing new proposed HHS guidelines designed to encourage universities to “police” financial arrangements between investigators and private sponsors and “to reduce or eliminate their own conflicts of interest, including stock ownership in companies that support research on the campus”).

products that are the subject of research protocols.<sup>134</sup> These rules do not require IRBs to address conflicts of interest or require their disclosure to research subjects in consent documents. Nevertheless, some IRBs debate these issues, consider them as part of the risk-benefit discussion, and require the disclosure of conflicts to research subjects.<sup>135</sup> Individual academic institutions also enforce varying policies regarding the management or disclosure of conflicts of interest, some more stringent than federal regulations, but the lack of consensus on this issue remains problematic.<sup>136</sup>

In addition to institutional and industry pressures on IRB performance, changing expectations among research subjects and a rapidly developing consumerist attitude towards medical services (including experimental therapies)

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<sup>134</sup> 21 C.F.R. § 54.4 (2003); see also Nina M. Gussack & Karen McDonnell Suddath, *Clinical Trial Conflicts Apply to Investigators, Too*, NAT'L L.J., May 14, 2001, at C3. Companies submitting marketing applications for approval of drugs, devices, and biological products must identify all clinical investigators who conducted clinical trials of the product (including employees and non-employees of the company) and must submit a certification that discloses any of the following financial arrangements: compensation affected by the outcome of the study, significant equity interest in the sponsor of the study, proprietary interest in the tested product, and significant payments of other types from the sponsor. 21 C.F.R. § 54.4(a)(3)(i-v).

<sup>135</sup> See Brainard, *supra* note 133, at A33 (noting that only one-quarter of IRBs regularly address conflict-of-interest questions as part of research protocol review).

<sup>136</sup> See Bernard Lo et al., *Conflict-of-Interest Policies for Investigators in Clinical Trials*, 343 NEW ENG. J. MED. 1616 (2000) (surveying such policies at ten universities); 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, 1624-25 (2000) (finding that only 7% of medical schools and research institutions required disclosure of financial interests in published research reports); Hamilton Moses III & Joseph B. Martin, *Academic Relationships with Industry: A New Model for Biomedical Research*, 285 JAMA 933 (2001); Justin Gillis, *Panel Targets Conflicts in Medical Research*, WASH. POST, Sept. 24, 2002, at A9 (summarizing recommendations from the Association of American Medical Colleges). Several professional organizations also have proposed or adopted standards dealing with conflicts of interest. See, e.g., AM. SOC'Y OF GENE THERAPY, POLICY OF THE AMERICAN SOCIETY OF GENE THERAPY ON FINANCIAL CONFLICT OF INTEREST IN CLINICAL RESEARCH (2000), available at [http://www.asgt.org/position\\_statements/conflict\\_of\\_interest.html](http://www.asgt.org/position_statements/conflict_of_interest.html) (last visited July 1, 2004); ASS'N OF AM. MED. COLLEGES (AAMC), PROTECTING SUBJECTS, PRESERVING TRUST, PROMOTING PROGRESS—POLICY AND GUIDELINES FOR THE OVERSIGHT OF INDIVIDUAL FINANCIAL INTERESTS IN HUMAN SUBJECTS RESEARCH (2001), available at <http://www.aamc.org/members/coitf/> (last visited July 1, 2004); Kelch, *supra* note 128, at 285-86; *Conflict Rules Urged for Doctor Research*, N.Y. TIMES, Feb. 8, 2001, at A21. Medical journals also have attempted to reign in the negative effects of conflicts of interest, usually by requiring disclosure of relevant financial and professional relationships. See, e.g., Frank Davidoff et al., *Sponsorship, Authorship, and Accountability*, 286 JAMA 1232, 1233 (2001) (discussing publication ethics, and emphasizing that journals will not publish "studies that are conducted under conditions that allow the sponsor to have sole control of the data or to withhold publication"); Catherine D. DeAngelis et al., *Reporting Financial Conflicts of Interest and Relationships Between Investigators and Research Sponsors*, 286 JAMA 89 (2001); Jeffrey M. Drazen & Gregory D. Curfman, *Financial Associations of Authors*, 346 NEW ENG. J. MED. 1901 (2002) (reversing the *Journal's* previous policy of prohibiting authors with financial connections to a company from writing review articles or editorials about that company's products, and defending this reversal by asserting that a complete prohibition on financial connections unduly constrains the *Journal's* ability to provide the best information on novel therapies).

add to the complexities of IRB review. In 1997, Congress required that NIH establish a publicly-accessible database of all clinical trials for drugs designed to treat serious or life-threatening conditions,<sup>137</sup> and private websites with names like “Hopelink.com” and “Emergingmed.com” continue to proliferate.<sup>138</sup> Increased advertising of research protocols in print media and on television and radio improves clinical trial enrollment but may contribute to unrealistic expectations about prospective benefit.<sup>139</sup> With easy access to information about clinical trials, many patients now question their physicians about experimental therapies or pursue such opportunities independently.<sup>140</sup>

Patients enroll in clinical trials with high expectations and often in desperate medical circumstances. As explained above, however, many patients may not fully understand the distinction between standard medical treatment and experimental procedures, and they may not adequately appreciate the risks of forgoing the former in favor of the latter.<sup>141</sup> Litigation likely will increase in a climate of unrealistic patient expectations regarding experimental therapies for

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<sup>137</sup> 42 U.S.C. § 282(j) (2000). This database is now available through the Internet. See NIH, GOVERNMENT FUNDED CLINICAL TRIALS, available at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (last visited July 1, 2004); see also NAT'L CANCER INST., GOVERNMENT FUNDED CANCER TRIALS, available at <http://www.cancer.gov/clinicaltrials> (last visited July 1, 2004). In addition, several privately-funded clinical trials databases provide information about clinical trials that focuses as much on recruiting participants as on conveying information. See, e.g., MUSELLA FDN., CLINICAL TRIALS AND NOTEWORTHY TREATMENTS FOR BRAIN TUMORS, available at <http://www.virtualtrials.org> (last visited July 1, 2004); CENTERWATCH, CLINICAL TRIALS LISTING SERVICE, available at [www.centerwatch.com](http://www.centerwatch.com) (last visited July 1, 2004).

<sup>138</sup> These websites, financed by venture capital companies, provide free information to patients but charge pharmaceutical companies up to several thousand dollars per individual for locating research candidates with rare diseases. See Judith Newman, *Drug Trials Reach out for Patients (and Vice Versa) on the Web*, N.Y. TIMES, Feb. 27, 2001, at D5 (describing the rise of websites designed to help pharmaceutical and biotech companies locate patients afflicted with particular medical conditions for clinical trials). Web site advertising remains free of any direct oversight, for now. *Id.*

<sup>139</sup> See OFFICE OF INSPECTOR GENERAL, HHS, RECRUITING HUMAN SUBJECTS: PRESSURES IN INDUSTRY-SPONSORED CLINICAL RESEARCH, OEI-01-97-00195, 17 (2000), available at <http://oig.hhs.gov/oei/reports/oei-01-97-00195.pdf> (last visited July 1, 2004) (describing and criticizing current trends in research subject recruitment, including enrollment incentives to physicians and patient-directed advertising that promotes the therapeutic misconception). The media's tendency to overstate the significance of research results may further fuel patient optimism about the prospective therapeutic benefit of experimental therapies. *Id.* at 21. More generally, the media and the lay public often struggle to comprehend the published results of clinical research. See Ray Moynihan et al., *Coverage by the News Media of the Benefits and Risks of Medications*, 342 NEW ENG. J. MED. 1645, 1647-49 (2000) (finding that the lay media often provided incomplete information about research on new drug products); Jane E. Brody, *Separating Gold from Junk in Medical Studies*, N.Y. TIMES, Oct. 22, 2002, at F7.

<sup>140</sup> See Newman, *supra* note 138, at D5 (noting that some physicians “may . . . perceive [the web sites] as threats to their authority”).

<sup>141</sup> See *supra* notes 65-70 and accompanying text.

serious disease,<sup>142</sup> particularly when patients simultaneously fail to appreciate that physicians may play dual roles as clinicians and researchers.<sup>143</sup> These developments reinforce the importance of meaningful informed consent, which in turn adds to the IRB's review and supervisory burdens.

Finally, IRBs and clinical researchers are no longer viewed as above reproach. The recent surge in media coverage of injuries and deaths at prominent research institutions and the concurrent decision by regulatory entities to re-examine existing research protections suggest that significant changes lay ahead.<sup>144</sup> Ethicists and health care providers have begun to express concern about individual and institutional preoccupation with the financial and professional rewards of scientific discovery, conflicts of interest, problems with disclosure of risks to research subjects, and coercive recruiting tactics. Recent evaluations have identified a disturbing pattern of researcher noncompliance with important human subjects protections and a concomitant failure by IRBs to detect and correct deficiencies.<sup>145</sup> In the past two years, the FDA and OHRP have temporarily shut down research programs in at least seven institutions while they remediated a host of compliance problems.<sup>146</sup> In response to these and other apparent deficiencies in research oversight, the FDA and OHRP have begun to scrutinize more closely research institutions with a spotty history of regulatory compliance, while the media has brought these issues to the public's attention.

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<sup>142</sup> See Christopher K. Daugherty et al., *Quantitative Analysis of Ethical Issues in Phase I Trials: A Survey Interview Study of 144 Advanced Cancer Patients*, IRB, May-June, 2000 at 6, 10 (finding that 90% of advanced cancer patients believed that the Phase I trials in which they were enrolled would provide some medical benefit to them); see also Newman, *supra* note 138, at D5 (quoting a professor of medicine whose research suggests that cancer patients agree to participate in clinical trials "“primarily for therapeutic benefit . . . [a]nd the trials are not designed that way””).

<sup>143</sup> See Miller, *supra* note 121, at 425-26.

<sup>144</sup> See, e.g., HHS, PUB. NO. OEI-01-91-00191, INSTITUTIONAL REVIEW BOARDS: PROMISING APPROACHES (1998), available at <http://oig.hhs.gov/oei/reports/oei-01-97-00191.pdf> (last visited July 1, 2004); HHS Status Report, *supra* note 8, at 16-17 (discussing a proposed "reengineering" of the federal research oversight process); cf. Michalee C. Christian et al., *A Central Institutional Review Board for Multi-Institutional Trials*, 346 NEW ENG. J. MED. 1405, 1405-07 (2002) (describing a pilot project utilizing a centralized IRB to expedite the local review of multi-center trials for the National Cancer Institute).

<sup>145</sup> A recent study reviewed 1,000 spot checks carried out by the FDA. In the protocols examined, 213 researchers failed to obtain informed consent from research subjects; 364 researchers deviated from their approved research protocols; and 140 failed to report adverse reactions in their study subjects. George J. Annas, *Regs Ignored in Research*, NAT'L L.J., Nov. 15, 1999, at A20; Jon Cohen, *Clinical Trial Monitoring: Hit or Miss?*, 264 SCIENCE 1534, 1536 (1994); Sheila Kaplan & Shannon Brownlee, *Dying for a Cure*, U.S. NEWS & WORLD REP., Oct. 11, 1999, at 36. Other surveys also have found major deficiencies in IRB review and oversight at major research institutions. See HHS Report, *supra* note 8, at 4-9.

<sup>146</sup> For example, the IRBs and research operations at Duke University, the University of Pennsylvania, Johns Hopkins University, and other prestigious institutions have been shut down recently due to noncompliance with regulatory requirements governing human research. See David Heath, *Medical-Research Reform Gains Support*, SEATTLE TIMES, Aug. 5, 2001, at A1.

### III. CONSTRUCTING A LIABILITY CLAIM AGAINST AN IRB

The failure of IRBs to exercise reasonable care in the review and supervision of clinical research sometimes results in injury to human subjects. In addition to satisfying the minimal standards set forth in the research regulations described in Part II, IRBs must exercise substantial judgment about complex ethical and scientific issues and opportunities for negligence abound. Some research injury lawsuits are still framed as traditional malpractice claims against physicians using experimental procedures.<sup>147</sup> Although lawsuits naming IRBs as defendants remain relatively rare,<sup>148</sup> the inclusion of boards as parties has begun to increase. After examining the arguments supporting the recognition of an IRB duty of care to research subjects, this Part will review the sparse existing case law dealing with tort claims against these boards, consider the consequences of increased liability, and preview some of the future complexities of such litigation.

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<sup>147</sup> See, e.g., Edward T. Pound, *Federal Rules for Research on People Often Fail*, USA TODAY, Feb. 26, 2001, at A1 (describing a case in which two patients in Florida sued an ophthalmic surgeon claiming that his use of an experimental medical device to perform their corneal transplant surgery without their knowledge or consent constituted negligence). Although this particular suit does not appear to include a claim against the institution where the surgeries were performed (or its IRB), lawsuits involving experimental treatments are on the rise. Other ethically questionable research protocols have been subject to professional and public criticism but remain unlitigated. See, e.g., Marla Cone, *Critics Question Ethics of Pollutant Testing on Humans*, L.A. TIMES, Nov. 28, 2000, at A4. In this study, funded by the aerospace corporation Lockheed Martin, on perchlorate (a rocket fuel component) that apparently had leached into drinking water wells in California, healthy volunteers were paid \$1,000 to take pills daily for six months that contained perchlorate at levels 83 times higher than in the contaminated well water; the research participants were monitored for adverse effects. The study apparently was designed to persuade those responsible for setting national drinking water contamination standards that certain perchlorate levels in drinking water do not pose an unacceptable hazard. See *id.*

<sup>148</sup> See Hoffman, *supra* note 76, at 746 (speculating that plaintiffs' lack of understanding about the role of IRBs in research, or concerns about establishing causation, may reduce the likelihood of lawsuits against IRBs). No court has yet found individual IRB members liable for injuries to research subjects, though several suits have been filed naming individual members in the complaint. See, e.g., *Kershaw v. Reichert*, 445 N.W.2d 16 (N.D. 1989) (affirming dismissal of claims against IRB members, hospital, and doctors in an informed consent case); *Complaint, Guckin v. Nagle*, 2002 WL 32151766 (Pa. Ct. Com. Pl. 2002) (No. 001425), available at 2002 WL 32151766 (alleging that IRB members were negligent in approving the study as designed, in approving the informed consent document, and in failing to monitor the consent process and the ongoing trial). Lawsuits naming individual IRB members would necessitate an individualized inquiry into each member's compliance with the applicable standard of care. See Linda M. Bordas, Note, *Tort Liability of Institutional Review Boards*, 87 W. VA. L. REV. 137, 148-49 (1984) (discussing the "diversity of expertise of members within a single IRB," and speculating that "[a]n IRB member whose expertise is in the same field as the investigator whose protocol is being reviewed . . . could be held liable for information which he knew, or should have known, in light of his special skill or knowledge"); see also John A. Robertson, *The Law of Institutional Review Boards*, 26 UCLA L. REV. 484, 533-34 (1979) (discussing the liability of individual IRB members).

A. *Finding a Duty of Care and Defining Its Scope*

Under general tort principles, a court first must conclude that the defendant owes a duty of care to the plaintiff before inquiring into the question of the defendant's negligence. The existence of a duty of care usually depends on some kind of direct relationship between plaintiff and defendant. Thus, absent some relationship with a patient, courts will not impose a duty of care on hospital employees.<sup>149</sup>

Lawsuits against individual researchers offer the easiest avenue for recognizing a tort-based duty of care. In some cases, a researcher who provides medical interventions to an individual in the context of a research protocol also has a doctor-patient relationship with that individual, and thus owes the patient-subject a duty of care in providing both standard therapies and experimental treatments.<sup>150</sup> Even without a therapeutic relationship, a court could conclude that a clinical investigator owes a duty of care to a research subject based on a fiduciary relationship between the two parties.<sup>151</sup> Because the subject looks to the investigator as an expert and places his trust in the investigator's expertise, the duty of care in this case would appear to include not only an obligation to act

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<sup>149</sup> For example, in *Clarke v. Hoek*, 219 Cal. Rptr. 845 (Ct. App. 1985), the plaintiff claimed that the defendant physician was negligent when he failed to intercede to prevent malpractice while proctoring a surgical procedure, which was done as part of the hospital's procedure to evaluate a surgeon for staff privileges. The court affirmed summary judgment for the defendant, explaining that his role was merely that of an observer, that he had no doctor-patient relationship with the plaintiff, and that his presence during the surgery served a separate purpose. *Id.* at 850.

<sup>150</sup> In cases dealing with informed consent in research, the plaintiff has received an experimental therapy, perhaps in combination with standard therapies, as a patient rather than as a participant enrolled in a formal research protocol. *See, e.g., Estrada v. Jaques*, 321 S.E.2d 240, 254 (N.C. Ct. App. 1984) (reversing summary judgment granted to surgeons who allegedly had failed to obtain informed consent from the plaintiff prior to performing experimental surgery to repair an aneurysm, and observing that health care providers who offer experimental treatments to their patients must exercise reasonable care under the circumstances, including informing the patient of the experimental nature of the proposed intervention); *see also* Noah, *supra* note 56, at 375-76 (discussing *Estrada* and similar cases).

<sup>151</sup> *See* Roger L. Jansson, Comment, *Researcher Liability for Negligence in Human Subject Research: Informed Consent and Researcher Malpractice Actions*, 78 WASH. L. REV. 229, 241-43 (2003) (describing the special relationship between researchers and subjects, and arguing that it should serve as the foundation for a researcher duty of care); *cf. Stiver v. Parker*, 975 F.2d 261, 268 (6th Cir. 1992) (imposing an affirmative duty of care on a surrogacy broker based on the special relationship between broker and surrogate); *Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479, 484-85 (Cal. 1990) (explaining that "a physician who treats a patient in whom he also has a research interest has potentially conflicting loyalties," and concluding that the researcher in the case owed a fiduciary duty of care to the patient that included disclosure of his personal interests in the research that might affect his medical judgment). Some courts have recognized that a researcher who provides a medical intervention to a patient-subject as part of a protocol is not functioning as the patient's physician but, despite this conclusion, have held the researcher responsible for injuries to the patient-subject arising from the research intervention. *See, e.g., Burton v. Brooklyn Doctors Hosp.*, 452 N.Y.S.2d 875, 879 (N.Y. App. Div. 1982).

reasonably under the circumstances but also a duty to take whatever steps are necessary to protect the subject's best interests.

Even in the absence of either a doctor-patient or an investigator-subject relationship, a court might decide that a researcher working in a hospital-directed research protocol has a duty to conform to the legal standard of reasonable conduct. For example, one court held that a researcher heading a hospital's retrospective study of radiation therapy safety had a duty to warn the plaintiff, a former hospital radiation therapy patient, of an increased risk of cancer, despite the absence of any direct relationship between the plaintiff and defendant.<sup>152</sup> As a practical matter, however, some researchers—Ph.D. candidates and post-doctoral fellows in particular—may not carry liability insurance and may lack extensive personal assets, so injured research subjects may wish to look higher up the chain of research oversight for a more promising defendant.

Holding IRBs, and the institutions that house them, responsible in tort for injuries to research subjects would stretch the boundaries of conventional tort doctrine still further. As with other traditional negligence actions, courts first would have to determine, as a matter of law, whether IRBs and the institutions in which they operate owe a duty of care to research participants that might support a finding of liability. In cases where courts conclude that such a duty exists, they must then define its scope and consider whether the IRB breached this duty of care.

How might a court justify a conclusion that an IRB—a relatively distant entity with no direct relationship to research subjects—owes a duty of care to these individuals? Courts typically consider a variety of factors in deciding whether a duty of care exists in a particular context.<sup>153</sup> Although no contractual relationship exists between an IRB and subjects of research conducted by an unrelated investigator, the subjects are intended third-party beneficiaries of the agreements between the institution, the board, and the researcher.<sup>154</sup> In the research setting, a

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<sup>152</sup> *Blaz v. Michael Reese Hosp. Found.*, 74 F. Supp. 2d 803, 805-07 (N.D. Ill. 1999).

<sup>153</sup> See, e.g., *Rowland v. Christian*, 443 P.2d 561, 564 (Cal. 1968) (suggesting considerations such as "the foreseeability of harm to the plaintiff, . . . the closeness of the connection between the defendant's conduct and the injury suffered, . . . [and] the policy of preventing future harm"); *Jaworski v. Kiernan*, 696 A.2d 332, 336-37 (Conn. 1997) (considering factors beyond foreseeability, including expectations of participants, in determining the duty of care owed to co-participants in recreational sports competition); *Largosa v. Ford Motor Co.*, 708 N.E. 2d 1219, 1221 (Ill. App. Ct. 1999) (considering several factors affecting the duty of care a business operator in close proximity to the highway owes to motorist); *Hopkins v. Fox & Lazo Realtors*, 625 A. 2d 1110, 1116 (N.J. 1993) (using a fairness test to determine the duty of care owed by realtors to attendees of open house).

<sup>154</sup> Cf. *Hand v. Tavera*, 864 S.W.2d 678 (Tex. Ct. App. 1993) (describing a triangular relationship between patient, health plan, and plan physician, and concluding that the plan physician owed the patient a duty of care despite the lack of direct contact between him and the patient); Lori A. Alvino, Note, *Who's Watching the Watchdogs? Responding to the Erosion of Research Ethics by Enforcing Promises*, 103 COLUM. L. REV. 893, 921-23 (2003) (advocating contract-based lawsuits on the theory that research subjects are intended beneficiaries of an IRB's Federal Wide Assurance agreement to adhere to federal regulations).

court might reason that the IRB voluntarily has undertaken the task of protecting research subjects (even if they do not know this) and in fact exists solely for that purpose; that it has undertaken to protect an identifiable and limited class of individuals (future enrollees in the study); and that the protected group reasonably relies on that IRB to provide responsible research oversight.<sup>155</sup>

In addition, public policy arguments support the imposition of a duty of care on IRBs. Although institutions typically furnish necessary medical care to treat research subject injuries free of charge, the current regulatory system permits institutions to refuse to provide financial compensation for injuries incurred during research procedures. That fact, combined with the reality that some researchers are likely to be judgment-proof, while their institutions have significant resources and derive financial rewards from the research, supports an argument that IRBs and/or the institutions that house them should provide appropriate compensation.<sup>156</sup> Courts also might consider the fact that most IRBs are “local” boards, familiar with the particular conditions of the institution in which the research is conducted, and that IRBs therefore have the best opportunity to supervise and control research conduct. Finally, the deterrent function of tort liability may provide the strongest justification for holding IRBs to a duty of care.<sup>157</sup> Research injury litigation threatens IRBs and the institutions that house them with significant damage judgments, the loss of public trust, and the loss of research funding dollars. The

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<sup>155</sup> Of course, this quasi-contract argument is somewhat problematic given that many research subjects do not understand the distinction between standard therapy and experimental treatment, may not recognize that they have enrolled in a research protocol, and may never have heard of the IRB. But at least some participants understand that research is subject to oversight and trust the process to protect them. With respect to commercial IRBs, patients do not receive standard or experimental therapies from the institution in which the IRB is housed. Therefore, the duty, if it exists, must rest solely on the notion that the commercial IRB has specifically undertaken to protect an identifiable class of prospective research subjects and that the class of protected subjects in some way relies on this protection.

<sup>156</sup> See Wendy K. Mariner, *Compensation for Research Injuries*, in 2 WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES 113 (Anna C. Mastroianni et al., eds. 1994) (arguing in favor of providing compensation to all injured research participants through a workers’ compensation type of system in addition to permitting individual negligence actions); Bernard R. Adams & Marilyn Shea-Stonum, *Toward A Theory of Control of Medical Experimentation with Human Subjects: The Role of Compensation*, 25 CASE W. RES. L. REV. 604, 637-47 (1975) (arguing for the establishment of a system of research injury compensation modeled after workers’ compensation laws).

<sup>157</sup> Some commentators express skepticism that tort liability provides any great level of deterrence to malpractice. See, e.g., Gary T. Schwartz, *Reality in the Economic Analysis of Tort Law: Does Tort Law Really Deter?*, 42 UCLA L. REV. 377, 397-402 (1994); but cf. Mary R. Anderlik & Nanette Elster, *Lawsuits Against IRBs: Accountability or Incongruity?*, 29 J. L. Med. & Ethics 220, 225 (2001) (observing that lawsuits against IRBs “[are] a perfectly ordinary means for ensuring that people and institutions meet their responsibilities” and that “given the slow pace of the response to recommendations from . . . critics of the IRB system, lawsuits may be one of the few ways of expediting the needed changes, as fear can often be a motivating force”); Michelle M. Mello & Troyen A. Brennan, *Deterrence of Medical Errors: Theory and Evidence for Malpractice Reform*, 80 TEX. L. REV. 1595, 1603-18 (2002).

possibility of liability for research injuries may encourage IRBs and institutions to invest more resources—in the form of money and human support—in order to avoid such losses.

In other contexts, courts have concluded that a duty of care exists even when a defendant is one or more steps removed from the plaintiff. For example, courts routinely have recognized that hospitals may owe a duty of care to patients to supervise physicians conducting activities within their facilities. Patients can, for example, sue hospitals when their credentialing committees do a poor job of selecting and then monitoring the quality of care delivered by physicians with staff privileges,<sup>158</sup> which resembles decisions by IRBs to review and approve the proposed research protocols of researchers at an institution.<sup>159</sup> Similarly, the hospital's duty of care with respect to staff privileges includes an obligation to investigate reports of substandard care or misconduct,<sup>160</sup> which resembles an IRB's

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<sup>158</sup> See, e.g., *Darling v. Charleston Cmty. Mem'l. Hosp.*, 211 N.E.2d 253, 257 (Ill. 1965) (recognizing that hospital licensing regulations and private accreditation standards may be used to define the hospital's duty of care to its patients); *Albain v. Flower Hosp.*, 553 N.E.2d 1038, 1046-47 (Ohio 1990) (holding that hospitals have a qualified duty of care in granting staff privileges and retaining only competent physicians, but explaining that hospitals need not "constantly supervise and second-guess the activities of its physicians, beyond the duty to remove a known incompetent"); *Strubhart v. Perry Mem'l. Hosp. Trust Auth.*, 903 P.2d 263, 276 (Okla. 1995) (holding that "the doctrine should generally be limited to imposing a duty of ordinary care on hospitals to ensure that: (1) only competent physicians are granted staff privileges, and (2) once staff privileges have been granted to a competent physician the hospital takes reasonable steps to ensure patient safety when it knows or should know the staff physician has engaged in a pattern of incompetent behavior"); *Johnson v. Misericordia Cmty. Hosp.*, 301 N.W.2d 156, 175 (Wis. 1981) (holding that "the hospital's failure to exercise that degree of care, skill and judgment that is exercised by the average hospital in approving an applicant's request for privileges is negligence" but that "[t]his is not to say that hospitals are insurers of the competence of their medical staff, for a hospital will not be negligent if it exercises the noted standard of care in selecting its staff"); see generally H. Ward Classen, *Hospital Liability for Independent Contractors: Where Do We Go From Here?*, 40 ARK. L. REV. 469 (1987) (investigating the doctrine of vicarious liability and the independent contractor exception); Martin C. McWilliams, Jr. & Hamilton E. Russell, III, *Hospital Liability for Torts of Independent Contractor Physicians*, 47 S.C. L. REV. 431 (1996) (reviewing the national movement toward increased hospital liability for independent contractor malpractice); David H. Rutchik, Note, *The Emerging Trend of Corporate Liability: Courts' Uneven Treatment of Hospital Standards Leaves Hospitals Uncertain and Exposed*, 47 VAND. L. REV. 535 (1994); but cf. Frances H. Miller, *Health Care Information Technology and Informed Consent: Computers and the Doctor-Patient Relationship*, 31 IND. L. REV. 1019, 1040 (1998) (observing that "[i]t may only be a matter of time . . . until the accumulation of legislative, accreditation, hospital by-law and other requirements motivate all hospitals to take on much the same direct responsibility to patients regarding informed consent . . . [as they have] assumed concerning clinical practice").

<sup>159</sup> Courts have recognized that modern hospitals include "an amalgam of many individuals not all of whom are licensed medical practitioners . . . [and that] at times a hospital functions far beyond the narrow sphere of medical practice." *Greenberg v. Michael Reese Hosp.*, 415 N.E.2d 390, 395 (Ill. 1980).

<sup>160</sup> *Purcell v. Zimbelman*, 500 P.2d 335, 343 (Ariz. Ct. App. 1972) (finding it reasonably probable that the negligent surgical procedure would not have been undertaken had the hospital taken action against the doctor who the hospital knew or should have known was incompetent); *Insinga v. LaBella*, 543 So. 2d 209, 214 (Fla. 1989) (imposing duty on hospitals to select and retain competent staff

obligation to engage in periodic monitoring of ongoing research. Interestingly, securing informed consent, which is at the core of efforts to hold IRBs accountable, is not typically included in this expanded duty of hospitals.<sup>161</sup>

Cases outside of the health care context also support the imposition of a duty of care based on various types of special relationships. Recent corporate scandals have generated a surge of interest in appropriate accounting standards, including the obligations of accountants to third parties who rely on audits when making investment decisions. Some commentators have argued in favor of recognizing the existence of a duty of care from accountants to third-party shareholders,<sup>162</sup> which provides support for a parallel IRB duty of care to third-party research subjects. Courts have adopted a variety of approaches to the question of liability of an accountant to a third-party investor or shareholder.<sup>163</sup> Although traditionally courts

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physicians, and commenting that “[t]his view is justified because the hospital is in a superior position to supervise and monitor physician performance and is, consequently, the only entity that can realistically provide quality control”); *Corleto v. Shore Mem’l. Hosp.*, 350 A.2d 534 (N.J. Super. Ct. Law Div. 1975) (hospital can be held negligent for improperly investigating an applying physician’s competence or for failing to take action against physicians on staff after potential problems with medical practice became apparent); *Campbell v. Pitt County. Mem’l. Hosp.*, 352 S.E.2d 902, 907-09 (N.C. Ct. App. 1987) (holding hospital liable for failure to establish effective mechanism for prompt reporting of situation creating threat to patients’ health); *Strubhart*, 903 P.2d 263. When hospitals make staff privilege decisions about physicians, some courts have recognized that hospitals owe a duty of care to future patients because the granting of privileges represents a certification that the physician will provide safe, non-negligent care to prospective patients. *See, e.g., Welsh v. Bulger*, 698 A.2d 581, 586 (Pa. 1997).

<sup>161</sup> *See, e.g., Ward v. Lutheran Hosp. & Homes Soc’y of Am.*, 963 P.2d 1031 (Alaska 1998) (holding hospital not liable for physicians’ failure to obtain informed consent because physicians were independent contractors selected by patient); *Petriello v. Kalman*, 576 A.2d 474, 477-79 (Conn. 1990) (holding that a hospital had no duty to obtain patient’s informed consent for surgery to be performed by a non-employee physician); *Smith v. Gaynor*, 591 A.2d 834, 835 (Conn. Super. Ct. 1991) (holding that a hospital does not have a duty to obtain patient’s informed consent for surgery unless attending physician is an employee or agent of the hospital).

<sup>162</sup> *See, e.g., Roger J. Buffington, A Proposed Standard of Common Law Liability for the Public Accounting Profession*, 5 S. CAL. INTERDISC. L.J. 485 (1997); Jay M. Feinman, *Liability of Accountants for Negligent Auditing: Doctrine, Policy, and Ideology*, 31 FLA. ST. U. L. REV. 17 (2003) (surveying different state approaches to auditor liability and noting that the question of liability to third parties remains unresolved in many jurisdictions); Melissa Harrison, *The Assault on the Liability of Outside Professionals: Are Lawyers and Accountants Off the Hook?*, 65 U. CIN. L. REV. 473 (1997) (concluding that outside professionals largely do not face liability for actions of corporate clients); Frank Partnoy, *Barbarians at the Gatekeepers?: A Proposal for a Modified Strict Liability Regime*, 79 WASH. U. L.Q. 491 (2001) (proposing a modified strict liability regime whereby banking, accounting, and law firms as gatekeepers would be strictly liable for any securities fraud damages paid by their clients pursuant to settlement or judgment).

<sup>163</sup> *See Christine M. Guerci, Annotation, Liability of Independent Accountant to Investors or Shareholders*, 48 A.L.R.5th 389 (1997 & Supp. 2003). In these cases, courts have looked to the Generally Accepted Auditing Standards (GAAS) and Generally Accepted Accounting Principles (GAAP), along with other industry standards, in defining the standard of care. *See Jodi B. Scherl, Evolution of Auditor Liability to Noncontractual Third Parties: Balancing the Equities and Weighing the Consequences*, 44 AM. U. L. REV. 255, 259-61 (1994). Traditionally, the accountant who complies in good faith with the GAAS and GAAP standards satisfies the general duty of care. *See id.* at 262; *see*

required privity of contract, or a client relationship between the accountant and the investor,<sup>164</sup> some courts have considered claims that investors or shareholders who rely on an accountant's audits or reports may recover damages, despite the lack of a client relationship or privity with the accountant, where there is fraud or gross negligence.<sup>165</sup> Under this theory of accountant liability, a shareholder could sue not only the corporation that misled him, but also the accountant that provided reports that facilitated or supported the misleading claims. Courts reasonably might accept similar rationales to address concerns about the lack of a direct relationship between IRBs and research subjects.

It is important, however, to consider the consequences of expanded IRB liability on medical innovation and health care. As growing numbers of human subjects participate in clinical research, and as clinical trials become a more common vehicle for delivering medical care, research-related injuries will increase, as will the stakes in research oversight. Some argue that the threat of tort liability could paralyze IRBs and could have a significant chilling effect on clinical research.<sup>166</sup> IRBs also may respond to the increased risk of liability by demanding that researchers comply with unnecessarily restrictive measures, just as physicians sometimes practice "defensive medicine" to prevent lawsuits.<sup>167</sup> The imposition of liability on IRBs in order to compensate individual research participants for

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*also* SEC v. Arthur Young & Co., 590 F.2d 785, 788 (9th Cir. 1979); Rhode Island Hosp. Trust Nat'l Bank v. Swartz, Bresenoff, Yavner & Jacobs, 455 F.2d 847, 851 (4th Cir. 1972); United States v. Simon, 425 F.2d 796, (2d Cir. 1969).

<sup>164</sup> See, e.g., Bily v. Arthur Young & Co., 834 P.2d 745, 767 (Cal. 1992) (rejecting claims against an accounting firm brought by third parties who foreseeably relied on the audit, and concluding that the traditional requirement of privity was appropriate, but acknowledging that third parties who are "specific intended beneficiaries" of an audit who are known to the auditor may recover on a theory of negligent misrepresentation).

<sup>165</sup> See RESTATEMENT (SECOND) OF TORTS § 552 (1977) (recognizing liability to third parties for negligence if information is provided "for the guidance of a third party," or for the use of a class of individuals of which the third party is a member and was justifiably relied upon in a type of transaction in which the accountant's representations were intended to have an effect); see also Security Pac. Bus. Credit v. Peat Marwick Main & Co., 597 N.E.2d 1080, 1083-86 (N.Y. 1992) (discussing how much contact between a third party and an auditor is sufficient to sustain a claim of liability, and concluding that a single or isolated contact with a third party represents an insufficient basis on which to bring such a claim); Guerci, *supra* note 163, at 404 n.7.

<sup>166</sup> See Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1847 (1996) ("[G]iving IRBs greater responsibility might well make their members more cautious. This will surely be true until the question of their potential liability for injuries suffered by trial subjects is resolved."); see also Richard A. Epstein, *Legal Liability for Medical Innovation*, 8 CARDOZO L. REV. 1139, 1156 (1987) (suggesting that tort actions "for injuries sustained because of departures from the experimental design" may be appropriate but that "it is mischievous, or worse, to look behind the experimental design after the fact when the outcomes are bad, as they often will be" because "the gains from experimental work can easily be dissipated by lawsuits that depend upon second-guessing the myriad difficult choices necessary for any experimental design").

<sup>167</sup> See Robertson, *supra* note 148, at 535.

injuries may not justify the societal consequences of a research slowdown,<sup>168</sup> but this question deserves fuller consideration.

The scant research injury case law includes suits against clinical researchers, hospitals, and IRBs, but it provides only superficial discussion about the existence of an IRB or institutional duty of care to research subjects. Although a few courts already have reached the conclusion that an IRB duty of care exists, the opinions tend to start with a discussion of IRB negligence in failing to protect a research subject from injuries and then work backwards to announce, or more often simply assume, the existence of a duty of care.

Courts ordinarily impose on physicians the general duty to obtain informed consent from his or her patients. A number of courts have declined to assign a separate duty of care to hospitals when a physician fails to obtain patient consent, particularly when the physicians are not employees,<sup>169</sup> and this includes failures to secure consent to experimental interventions.<sup>170</sup> A few courts, however, have held

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<sup>168</sup> In recognition of these concerns, the Maryland legislature enacted a statute requiring researchers to conduct their research in compliance with federal regulations. The law also requires IRBs to make their meeting records available for public scrutiny. MD CODE ANN., HEALTH GEN. § 13-2001 - 04 (Supp. 2003); H.B. 917, 2002 Leg., 416<sup>th</sup> Sess. (Md. 2002); see also David Nitkin, *Senate OKs Bill to Tighten Rules on Human Research; Governor Expected to Sign Legislation*, BALT. SUN, Apr. 6, 2002, at B1 (reporting on the Maryland General Assembly's move to tighten regulations for experiments involving human subjects), available at 2002 WL 6955100; Matthew Mosk, *Research Shield Discussed in Maryland*, WASH. POST, Oct. 24, 2001, at B7 (explaining that the legislature considered the compliance defense in response to the *Grimes* decision, which some legal experts argue "threaten[s] to undermine legitimate medical research"). Congress has granted tort immunity to persons serving on IRB-like panels, such as Professional Standards Review Organizations (PSROs). 42 U.S.C. § 1320c-6(b) (2000); see also *Kwoun v. Southeast Mo. Prof'l Stds. Org.*, 811 F.2d 401, 412 (8th Cir. 1987); Health Care Quality Improvement Act, 42 U.S.C. §§ 11111-11152 (2000). Just as public hospitals and their employees are subject to suit, IRBs in public institutions would not receive any special protection from tort suits, unless they are deemed to be engaging in a discretionary policymaking function. See, e.g., *Kan. Atty. Gen. Op. No. 81-139* (1981); *Va. Code Ann. §8.01-44.1* (2000) (providing immunity from suit for individual IRB members). And of course, many IRBs exist in private institutions or as freestanding bodies.

<sup>169</sup> See, e.g., *Ward v. Lutheran Hosp. & Homes Soc'y of Am., Inc.*, 963 P.2d 1031, 1034 (Alaska 1998) (hospital had no duty to obtain informed consent for blood transfusion ordered by patient's physician); *Krane v. St. Anthony Hosp. Sys.*, 738 P.2d 75, 77 (Colo. Ct. App. 1987) (explaining that even where an employee surgical nurse was negligent, "[i]t is the surgeon, and not the hospital, who has the technical knowledge and training necessary to advise each patient of the risks of the surgery" and that "the hospital does not know the patient's medical history, nor the details of the particular surgery to be performed"); *Petriello v. Kalman*, 576 A.2d 474, 477-78 (Conn. 1990) (exonerating the hospital even though an employee nurse had violated the institution's policy of ensuring signature of a consent form prior to surgery); *Lincoln v. Gupta*, 370 N.W.2d 312, 318 (Mich. Ct. App. 1985) (private physician, not hospital, had duty to warn patient of the risks of cardiac catheterization); *Cox v. Haworth*, 283 S.E.2d 392, 394-96 (N.C. Ct. App. 1981) (holding that hospital had no duty to obtain informed consent from patient for a myelogram when the procedure was performed by a non-employee physician).

<sup>170</sup> See, e.g., *Femrite v. Abbott Northwestern Hosp.*, 568 N.W.2d 535, 543 (Minn. Ct. App. 1997) (holding that it is the physician's responsibility, not the hospital's, to obtain informed consent in the context of experimental treatments or clinical trials); *Fiorentino v. Wenger*, 227 N.E.2d 296, 301 (N.Y. 1967) (concluding that "the hospital . . . should not share in the responsibility to advise patients of the

that institutions participating in clinical trials may share legal responsibility for informed consent lapses. When an institution undertakes to specify consent requirements for research performed under an IRB's supervision, courts have concluded that the institution can be held responsible for ensuring that the consent is meaningful and complete.<sup>171</sup>

Where regulations are designed to provide special protection for a class of persons who are not otherwise able to protect themselves, courts sometimes will imply a duty of care based on these regulations.<sup>172</sup> In one case, the plaintiff was injured by an intraocular lens implanted in his eye as part of an investigational protocol to determine the product's safety.<sup>173</sup> The surgeon never informed the patient that the device was experimental or that the surgery comprised part of a research protocol to test the safety and effectiveness of the device. Although the appellate court recognized that, under the state's common law, the physician rather than the hospital ordinarily has the duty to obtain consent for a medical procedure, the court noted that:

the facts of this case are quite different for we are not here addressing the duty owed by a physician to a patient but rather a duty owed by the hospital to the patient. In this instance, the hospital, as a participant in a clinical investigation . . . specifically assumed a duty to ensure that informed consent was obtained by any patient participating in the study.<sup>174</sup>

Interestingly, the court used the federal regulations governing IRBs to imply a duty running to patients that did not otherwise exist at common law,<sup>175</sup> even though the

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novelty and risks attendant on the procedure"—in this case a highly experimental surgical procedure); *Stewart v. Cleveland Clinic Found.*, 736 N.E.2d 491 (Ohio Ct. App. 1999) (concluding that investigator and institution may have failed to satisfy their common law duty to secure informed consent notwithstanding the IRB's apparent approval of the consent form).

<sup>171</sup> See, e.g., *Kus v. Sherman Hosp.*, 644 N.E.2d 1214, 1220-21 (Ill. App. Ct. 1995) (finding that by becoming a participating institution in the study, the hospital is charged with assuring the adequacy and effectiveness of the informed consent obtained); *Friter v. Iolab Corp.*, 607 A.2d 1111, 1113 (Pa. Super. Ct. 1992) (holding that "the hospital, as a participant in a clinical investigation for the FDA, specifically assumed a duty to ensure that an informed consent was obtained"); *Weiss v. Solomon*, 1989 R.J.Q. 731 (Can.) (holding IRB liable for failing to ensure adequate consent and for failing to limit the selection of subjects appropriately); cf. *Bryant v. HCA Health Servs. of No. Tenn.*, 15 S.W.3d 804, 810-11 (Tenn. 2000) (explaining that "a hospital . . . may assume an independent legal duty to obtain the informed consent of a patient undergoing a procedure that is part of an investigational study monitored by the FDA").

<sup>172</sup> See RESTATEMENT (SECOND) OF TORTS § 874A (1977).

<sup>173</sup> See *Friter*, 607 A.2d, at 1111.

<sup>174</sup> *Id.* at 1113.

<sup>175</sup> *Id.* at 1114 (noting that, "under applicable federal regulations, . . . [the hospital] had an affirmative duty to 'assure that the rights of human subjects are properly protected, that legally effective informed consent is obtained, and that the methods of obtaining consent properly informs the human subject of the significant aspects of the study'"). A few courts use federal requirements to trigger a duty under state law that otherwise does not exist, but this is a fairly unusual approach. See *Lars Noah*,

regulations do not themselves provide an express or implied right of action.<sup>176</sup> In a similar case, another court held that a hospital and its IRB could be liable for failure to obtain proper informed consent prior to the implantation of an experimental intraocular lens, because the hospital was a participant in research subject to federal regulations requiring such consent.<sup>177</sup>

Finally, although they do not create a private right of action under federal law, the human subjects protection regulations appear to contemplate the existence of a common law duty of care from IRBs to research subjects. The informed consent rules provide in part that no exculpatory language may be used in an attempt to “waive any of the subject’s legal rights” or to “release the investigator, the sponsor, the institution, or its agents from liability for negligence.”<sup>178</sup> The regulation thereby presumes that someone other than the investigator—namely, the institution or its IRB—could be liable in negligence for injury to a research subject. Indeed, even without such a regulatory prohibition, courts probably would refuse to enforce such exculpatory language.<sup>179</sup>

Another recent decision provides more explicit support for the trend of judicial recognition of an IRB duty of care. In *Grimes v. Kennedy Krieger*

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*Advertising Prescription Drugs to Consumers: Assessing the Regulatory and Liability Issues*, 32 GA. L. REV. 141, 167-68 (1997) (discussing the consequences of such an approach in the context of a different FDA requirement).

<sup>176</sup> See *Kershaw v. Reichert*, 445 N.W.2d 16, 17 (N.D. 1989) (concluding that the “FDA’s regulations adopted pursuant to the FDCA did not authorize a private action against hospitals, institutional review committees, or doctors” for injuries arising out of unsuccessful experimental procedures); see also *Bailey v. Johnson*, 48 F.3d 965, 967-68 (6th Cir. 1995); *Brinkman v. Shiley, Inc.*, 732 F. Supp. 33, 35 (M.D. Pa. 1989), *aff’d*, 902 F.2d 1558 (3d Cir. 1989); James M. Beck & John A. Valentine, *Challenging the Validity of FDCA-Based Causes of Action in the Tort Context: The Orthopedic Bone Screw Experience*, 55 FOOD & DRUG L.J. 389 (2000).

<sup>177</sup> See *Kus v. Sherman Hosp.*, 644 N.E.2d 1214, 1220-21 (Ill. App. Ct. 1995) (explaining that, “[b]y becoming a participating institution in this particular study, Sherman hospital was charged with assuring that ‘legally effective informed consent’ was obtained prior to the experimental surgery,” and concluding that the federal regulations governing informed consent and continuing review in research involving experimental devices imposed a duty on the hospital “to ensure that the form its IRB had promulgated was being used” and that, therefore, “a hospital, as well as a physician, may be liable for claims arising from the lack of informed consent”). But see *Kershaw*, 445 N.W.2d at 17 (affirming dismissal of claims against IRB members, hospital, and doctors in a case alleging negligent failure to obtain informed consent prior to implanting intraocular lenses).

<sup>178</sup> 21 C.F.R. § 50.20 (2003); 45 C.F.R. § 46.116 (2003); see also *Vodopost v. MacGregor*, 913 P.2d 779, 787 (Wash. 1996) (refusing to enforce an exculpatory clause in a case of non-therapeutic research).

<sup>179</sup> See, e.g., *Tunkl v. Regents of Univ. of Cal.*, 383 P.2d 441, 446-47 (Cal. 1963) (holding a hospital-patient contract which required the patient to release the hospital from liability for future negligence invalid); *Hartsell v. Ft. Sanders Reg’l Med. Ctr.*, 905 S.W.2d 944, 947 (Tenn. Ct. App. 1995) (holding that a signed consent form defeated a battery claim, but allowing plaintiff’s medical malpractice claim to proceed); *Emory Univ. v. Porubiansky*, 282 S.E.2d 903, 905 (Ga. 1981) (holding that a licensed dentist’s attempt to relieve himself of the duty of reasonable care by contract is invalid as against public policy); *Cudnik v. William Beaumont Hosp.*, 525 N.W.2d 891, 895-96 (Mich. Ct. App. 1994) (holding the hospital’s exculpatory agreement invalid as against public policy), see also *infra* notes 245-248 and accompanying text (discussing assumption of risk).

*Institute, Inc.*,<sup>180</sup> Maryland's highest court concluded that an institution, its IRB, and the PI owed a duty of care to research participants based on the nature of the relationship and the seriousness of the potential harm in the absence of due care.<sup>181</sup> Plaintiffs sued the Johns Hopkins IRB, alleging negligent review and approval of a non-therapeutic research protocol designed to determine whether incomplete lead paint abatement in housing occupied by children successfully reduced systemic lead levels in the children's blood.<sup>182</sup> At least two children who participated in the study allegedly suffered injuries from lead exposure.<sup>183</sup>

The court, relying on the standards in the federal research rules and the ethical duties of clinical investigators as detailed in the Nuremberg Code, noted that "the special relationship between research entities and human subjects used in the research will almost always impose duties,"<sup>184</sup> including, in this case, duties to notify and warn the participants promptly about the presence of lead in order to prevent exposure and to inform the participants fully about the risks of participation.<sup>185</sup> Commentators have correctly criticized the court for its overbroad approach to the legal questions presented and for its extreme rhetoric in comparing the lead paint research protocol with historical research atrocities such as the Nazi experiments and the Tuskegee Syphilis Study;<sup>186</sup> however for the reasons discussed earlier, the court's recognition of an IRB duty of care in tort has some merit.

Assuming that IRBs have a tort-based duty to protect research subjects, how far does it extend? Courts must calibrate the scope of the duty appropriately in order to address competing concerns about the effects of imposing such a duty on IRBs. The paucity of litigation against IRBs to this point leaves the question of the appropriate standard of care unresolved. Theoretically, courts simply could apply

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<sup>180</sup> 782 A.2d 807 (Md. 2001).

<sup>181</sup> *Id.* at 842-43 (noting that the duty included an obligation to inform the participants in a timely manner of the results of the research and of the potential risks and harms of participating). For a recent discussion of the researcher and IRB duty of care, see Diane E. Hoffmann & Karen H. Rothenberg, *Whose Duty Is It Anyway?: The Kennedy Krieger Opinion and Its Implications for Public Health Research*, 6 J. HEALTH CARE L. & POL'Y 109, 111-14 (2003) (describing the legal basis for a researcher's duty of care).

<sup>182</sup> The researchers encouraged or required landlords participating in the study to rent the properties to families with children, and the protocol required the children to remain on the premises for two full years in order to complete all of the required measurements. See *Grimes*, 782 A.2d at 811-13 (noting that "it was anticipated that the children, who were the human subjects in the program, would, or at least might, accumulate lead in their blood from the dust, thus helping the researchers to determine the extent to which the various partial abatement methods worked," and comparing this study design to the old practice of sending canaries into coal mines to detect the presence of poisonous gases).

<sup>183</sup> *Id.* at 818.

<sup>184</sup> *Id.* at 817.

<sup>185</sup> *Id.* at 835-37.

<sup>186</sup> See Hoffmann & Rothenberg, *supra* note 181, at 124-25 (describing the opinion's "one-sided and arguably exaggerated fact presentation").

a general standard of negligence—namely, an obligation to act reasonably under the circumstances. Because such an open-ended duty might impose unacceptable constraints on the progress of research, however, courts should attempt to place some more precise limitations on the scope of the duty.

One possible approach to narrowing the extent of an IRB's duty in tort would treat the federal regulations as fully defining the standard of care, meaning that a violation of a regulation would constitute negligence while compliance would provide a defense to liability.<sup>187</sup> The human subjects protection regulations tend to emphasize elements of structure and procedure, however, leaving the more complex scientific and ethical matters largely to the discretion of boards. Therefore, failures to abide by the regulations will not invariably establish negligence if the rules do not directly relate to questions of safety.<sup>188</sup> Moreover, the open-ended character of the regulations regarding matters of ethical interpretation, such as the propriety of placebo-controls,<sup>189</sup> or the payment of subjects for participation,<sup>190</sup> makes defining the scope of the IRB's duty solely by reference to regulations an unattractive option.

In the alternative, courts could evaluate whether an IRB's conduct conforms to customary practice, much as they do in medical negligence cases. In malpractice litigation, physicians usually need only demonstrate that they have complied with customary medical practice.<sup>191</sup> Under this approach, proof of compliance with IRB custom would be dispositive on the question of whether a particular board acted appropriately.<sup>192</sup> An injured research participant potentially could offer expert testimony, however, arguing that the prevailing custom among IRBs is substandard in some respect and should be more protective of research

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<sup>187</sup> For a discussion about the relative merits of a regulatory compliance defense in a related context, see Lars Noah, *Rewarding Regulatory Compliance: The Pursuit of Symmetry in Products Liability*, 88 GEO. L.J. 2147 (2000).

<sup>188</sup> See *infra* notes 206-207 and accompanying text.

<sup>189</sup> See *infra* notes 252-260 and accompanying text.

<sup>190</sup> See *supra* notes 71-75 and accompanying text.

<sup>191</sup> See, *Holt v. Godsil*, 447 So. 2d 191, 192-93 (Ala. 1984); *Hall v. Hilbun*, 466 So. 2d 856, 872-73 (Miss. 1985); *Senesac v. Assoc. in Obstetrics & Gynecology*, 449 A.2d 900, 902-03 (Vt. 1982). Nevertheless, noncompliance with custom sometimes will be excused in cases where a respectable minority of physicians behave differently. See, *DiFilippo v. Preston*, 173 A.2d 333, 337 (Del. 1961); *D'Angelis v. Zakuto*, 556 A.2d 431, 436 (Pa. Super. Ct. 1989). Courts generally require expert testimony to define customary medical practice. See, *Bell v. Hart*, 516 So. 2d 562, 570 (Ala. 1987); *Cox v. Dela Cruz*, 406 A.2d 620, 622 (Me. 1979); *Lundgren v. Eustermann*, 370 N.W.2d 877, 880 (Minn. 1985); *Harris v. Robert C. Groth, M.D., Inc.*, 663 P.2d 113, 118-19 (Wash. 1983); *Vassos v. Roussalis*, 658 P.2d 1284, 1288 (Wyo. 1983).

<sup>192</sup> Conversely, the plaintiff could offer expert testimony to demonstrate that the defendant IRB failed to comply with the customary conduct regarding, for example, the frequency of continuing review or the evaluation of complex trial design issues.

participants. This gambit occasionally succeeds in the medical malpractice context.<sup>193</sup>

In addition, under medical malpractice principles, physicians sometimes can invoke a “resource-based caveat” to a national standard of care.<sup>194</sup> IRBs also may attempt to apply this principle, arguing that inadequate manpower and institutional support prevented the board from fully exercising its supervisory duty for ongoing protocols or from reviewing new protocols as thoroughly as it might under better circumstances, but this explanation may very well fail to persuade a jury.<sup>195</sup>

The use of a medical malpractice type of customary standard also would pose other problems. Although the federal regulations provide some guidance about appropriate IRB operations, as these local boards have proliferated, many have developed different methods of operation that nevertheless comply with general regulatory procedures. In some instances, courts might find it nearly impossible to describe customary practice among IRBs because no nationwide practice has yet emerged.<sup>196</sup> Moreover, the genuine uncertainty inherent in research involving new

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<sup>193</sup> See *United Blood Servs. v. Quintana*, 827 P.2d 509, 520-26 (Colo. 1992) (holding that it should be a question of fact for the jury whether professional blood screening standards to detect the AIDS virus were adequate); *Helling v. Carey*, 519 P.2d 981, 983 (Wash. 1974) (holding that the customary practice of delayed screening for glaucoma was inadequate given the simplicity and low cost of the test and the consequences of not screening); *Nowatske v. Osterloh*, 543 N.W.2d 265, 272 (Wis. 1996) (“[S]hould customary medical practice fail to keep pace with developments and advances in medical science, adherence to custom might constitute a failure to exercise ordinary care.”); see also Philip G. Peters, Jr., *The Quiet Demise of Deference to Custom: Malpractice Law at the Millennium*, 57 WASH. & LEE L. REV. 163, 188 (2000).

<sup>194</sup> See, e.g., *Hall v. Hilbun*, 466 So. 2d 856, 872-73 (Miss. 1985) (explaining that the duty of care should be defined “based upon the adept use of such medical facilities, services, equipment and options as are reasonably available,” but adding that in some circumstances health care providers may have a duty to transfer the patient to a better-equipped facility); see also Barbara A. Noah, *The Managed Care Dilemma: Can Theories of Tort Liability Adapt to the Realities of Cost Containment?*, 48 MERCER L. REV. 1219, 1230-32 (1997) (suggesting that the malpractice standard of care is sufficiently elastic to cover services provided in managed care systems that impose cost-containment constraints on physicians). Similarly, IRBs must do the best they can with available resources for review, but they may have a duty, in certain cases, to call in special experts to assist in the review of particularly complex research, or to transfer their supervisory obligations to an IRB with adequate resources to review and supervise an unusually large multi-center trial.

<sup>195</sup> Courts generally have limited the “resource-based caveat” to claims against individual practitioners rather than institutions: hospitals must have “minimum facilities and support systems to treat the range of problems and side effects that accompany procedures they offer.” BARRY R. FURROW ET AL., HEALTH LAW § 7-3(a) (2000); see also *Hernandez v. Smith*, 552 F.2d 142 (5th Cir. 1977) (finding an obstetrical clinic that lacked equipment to perform caesarean sections liable for failing to provide minimal support facilities); *Horton v. Niagara Falls Mem’l. Med. Ctr.*, 380 N.Y.S.2d 116 (App. Div. 1976) (rejecting short staffing as a defense to a finding of liability for an injury to a patient). An injured research subject might make a similar claim against an institution that provides inadequate support for its IRB.

<sup>196</sup> And, because different IRBs review varying proportions of research in a variety of medical disciplines, comparing the operations of one local IRB to another may amount to comparing apples with oranges. Cf. Epstein, *supra* note 166, at 1154-55 (observing that “it is possible to develop a set of

medical technologies makes it difficult even for individual IRBs to develop a pattern or technique of review that rises to the level of custom.<sup>197</sup> A particular IRB's approach to questions such as the appropriateness of a proposed trial design, the use of placebo controls, or some other hotly debated ethical question in research, may leave courts with little guidance as to what is customary and, therefore, open the door to court-based standard setting, which itself could vary substantially.

Ideally, courts would adopt a third approach to define the contours of the IRB duty of care. Because actual customary practice remains inadequate, courts instead should describe the scope of the duty in terms of the aspirational standards set out in ethical guidelines such as the Nuremberg Code and the Declaration of Helsinki, layered onto the basic regulatory requirements.<sup>198</sup> The international research community created these guidelines through a thoughtful, collaborative approach, using the collective experience of scientists and ethicists, and they command significant respect among experts on clinical research ethics. Such an approach would create a higher standard of care than a simple regulatory compliance approach, while at the same time avoiding the adverse consequences of an open-ended general negligence standard.

As with the existence of a duty of care for IRBs, recent developments in corporate hospital liability law provide interesting parallels that may help to define the scope of the board's duty. The steady increase in hospital regulatory activity, through the development of hospital bylaws and private accreditation standards, has further refined the concept of institutional liability. Several courts have held that quasi-regulatory standards such as those of the Joint Commission on the Accreditation of Health Care Organizations (JCAHO) can be used as evidence of the standard of care to which the hospital should be held.<sup>199</sup> The human subjects protection regulations, together with the self-regulatory aspects of the ethical codes, should provide similar guideposts for courts as they review IRB conduct.

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metacustoms which are designed to deal with those particular gaps in knowledge, but these rules will have far less bite than specific directives about the use of given products or treatments").

<sup>197</sup> Cf. James A. Henderson, Jr. & John A. Siliciano, *Universal Health Care and the Continued Reliance on Custom in Determining Medical Malpractice*, 79 CORNELL L. REV. 1382, 1389-94 (1994) (discussing how the proliferation of new technologies in medicine undermines the common standard of medical practice and makes it more difficult to define the medical standard of care in a malpractice action).

<sup>198</sup> See *supra* notes 30-35 and accompanying text.

<sup>199</sup> See *Jackson v. Power*, 743 P.2d 1376, 1382-83 (Alaska 1987) (finding the source of the hospital's nondelegable duty to ensure the proper operation of its emergency rooms in JCAHO standards relating to the maintenance of emergency rooms); *Johnson v. Mountainside Hosp.*, 571 A.2d 318, 324 (N.J. Super. Ct. App. Div. 1990) (admitting portions of the JCAHO accreditation manual for hospitals into evidence); *Blanton v. Moses H. Cone Mem'l. Hosp.*, 354 S.E.2d 455, 458 (N.C. 1987) (holding that the failure of a hospital to enforce JCAHO standards constituted "some evidence" of negligence).

A few courts already have considered the propriety of relying on guidance from ethical codes in evaluating the conduct of clinical research. One court, in evaluating a tort claim for brain damage during simulated deep dive experiments in a hyperbaric chamber, concluded, based in part on ethical standards in the Nuremberg Code, that the researchers had not adequately disclosed the risks of the experiment.<sup>200</sup> A few other courts have discussed with approval ethics codes as sources of guidance on the scope of research duties in evaluating informed consent claims in research.<sup>201</sup> At least one court, however, has affirmed a trial court's refusal to admit the Belmont Report into evidence to document appropriate research conduct as part of a plaintiff's claim that the treating hospital subjected him to a medical experiment without his consent.<sup>202</sup> In any event, it seems likely that enterprising plaintiffs' lawyers will continue to explore novel causes of action, including claims based on dignitary harms and constitutional rights, that rely in part on the ethical standards set out in these codes of research conduct.<sup>203</sup>

In theory, ethical codes and statements can provide some useful additional guidance to courts, beyond that available in the federal regulations, in defining the nature and scope of the IRB duty of care. The application of such standards nevertheless will present certain challenges—submitting such complex ethical issues to a jury, for instance, raises a host of concerns. Juries will likely struggle to

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<sup>200</sup> *Whitlock v. Duke Univ.*, 637 F. Supp. 1463, 1470-72 (M.D.N.C. 1986) (describing the Nuremberg Code as "persuasive guidance on an appropriate standard of care" in the non-therapeutic experimentation context), *aff'd*, 829 F.2d 1340, 1343 (4th Cir. 1987).

<sup>201</sup> *See, e.g., Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807, 849 (Md. 2001) (holding that the "breach of obligations imposed on researchers by the Nuremberg Code might well support actions sounding in negligence in such cases as those at issue here"). A concurring judge in *Grimes* expressed concern that the opinion ranged well beyond the scope of the questions presented to the court and refused to join the majority in adopting the Nuremberg Code into state law. *See id.* at 858-61 (Raker, J., concurring in judgment).

<sup>202</sup> *See Ancheff v. Hartford Hosp.*, 799 A.2d 1067, 1079-80 (Conn. 2002) (concluding that the trial court did not abuse its discretion in determining that the Belmont Report would "unduly arouse [the jury's] emotions").

<sup>203</sup> One recent federal lawsuit alleges that clinical researchers and others associated with the melanoma vaccine trial at Oklahoma University Health Sciences Center breached the plaintiffs' "right to be treated with dignity." *See Complaint for Dawanna Robertson et al., Robertson v. McGee*, (N.D. Okla. 2001) (No. 01-CV-60), available at 2002 WL 535045.; *see also Milford, supra note 29*, at A13 (describing several lawsuits alleging new theories of liability, including "the claim that volunteers' rights to dignity include the right to be told the risks and benefits of an experiment; the right to an ethical experiment in which the benefits outweigh the risks; the right to be fully apprised of conflicts of interest (including financial stakes); and the right to be assured that the research is valid and valuable"). Plaintiffs' lawyers based these claims on both the Nuremberg Code and the Declaration of Helsinki, although neither of the passages from these two ethical statements, as excerpted in the complaint, explicitly announces such a right. *See Complaint for Dawanna Robertson et al., Robertson v. McGee*, (N.D. Okla. 2001) (No. 01-CV-60), available at 2002 WL 535045. The suit was recently dismissed for lack of federal court jurisdiction. *See Robertson v. McGee*, 2002 WL 535045 (N.D. Okla. 2002). Professor Jay Katz has suggested that the definition of "harm" in research should include "not only physical harm but also dignitary harm inflicted whenever subjects remain uninformed or inadequately apprised of the purposes and nature of the research project." Katz, *supra note 31*, at 404 n.9.

apply abstract philosophical principles such as autonomy and beneficence when evaluating claims of research misconduct.<sup>204</sup> In addition, where there is a genuine ethical controversy about the appropriateness of an IRB's decision to approve a particular study design, for example, the outcome of the case ultimately may depend on the dueling opinions of ethics experts whose assessment of customary IRB conduct may be drawn, inappropriately, from their limited local experiences.<sup>205</sup> The appropriate role of ethical codes and statements such as the Declaration of Helsinki, the Nuremberg Code, and the Belmont Report, in the judicial evaluation of an IRB's conduct will continue to evolve, but courts should continue to pay attention to the ethical principles embodied in these guidelines.

### B. *Examining Different Types of Breach*

Assuming that IRBs owe a tort-based duty of care to research participants, the more interesting question revolves around the process of establishing a breach of this duty. As existing case law and pending litigation demonstrate, claims of breach exist along a spectrum of complexity. At one extreme, blatant violations of the federal regulations may serve as evidence of breach of the standard of care. At the other end of the spectrum, plaintiffs may pursue far more complex claims, suggesting that IRBs breach the standard of care when they fail to exercise sound ethical judgment, notwithstanding compliance with the explicit requirements of the regulations. Some of the variations on breach presented in the latter half of this Part suggest that, if courts allow these sorts of lawsuits to proceed, they will struggle to establish some qualifications or outer boundaries on a duty of care for IRBs.

Once an injured plaintiff has established some common law duty running from the defendant IRB to the plaintiff, a board's violation of an explicit regulation governing human research can serve as evidence of negligence in most jurisdictions. It is less clear whether federal research regulations resemble classic safety regulations sufficiently to support a conclusion that any violation constitutes

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<sup>204</sup> See *Ancheff*, 799 A.2d at 1079-80 (opining that the admission of the Belmont Report into evidence would "tend to confuse the issues and mislead the jury" by inviting the jury to "engage in a highly abstract and philosophical level of inquiry into such subjects as respect for the autonomy of persons, . . . the concept of beneficence, and the various theories of justice").

<sup>205</sup> On the complexities of expert testimony on bioethics matters, see Edward J. Imwinkelried, *Expert Testimony by Ethicists: What Should Be the Norm?*, 76 TEMP. L. REV. 91, 99-100 (2003) (describing the current controversy over admitting bioethics testimony into evidence); Bethany Spielman & George Agich, *The Future of Bioethics Testimony: Guidelines for Determining Qualifications, Reliability, and Helpfulness*, 36 SAN DIEGO L. REV. 1043 (1999); see also Sheryl Gay Stolberg, *Bioethicists Find Themselves the Ones Being Scrutinized*, N.Y. TIMES, Aug. 2, 2001, at A1 (quoting professor of law and medical ethics Alta Charo, who explains that "anybody can stand up and claim to be an ethicist—there is no licensing, there is no accreditation").

negligence per se.<sup>206</sup> Many of the research regulations focus on IRB process and function rather than directly on research subject safety. To the extent that some IRB regulations resemble standards of procedure, rather than traditional safety regulations such as traffic laws, courts may hesitate to conclude that a board's deviation from the rules amounts to negligence per se. Nevertheless, when an injured plaintiff introduces evidence that an IRB or researcher committed an unexcused violation of an applicable human subjects protection regulation, such evidence certainly may prove helpful in making a case against a board.<sup>207</sup>

Not surprisingly, much of the existing research injury litigation focuses on explicit regulatory violations by the investigator, the IRB, or both, and recently filed lawsuits alleging negligence in research abound with examples of regulatory noncompliance.<sup>208</sup> Given the pattern of widespread infractions discussed in Part II, a plaintiff's lawyer will have little difficulty finding one or more arguable failures to comply in any particular case. For example, despite the explicit regulatory requirement that consent forms disclose which procedures in the research are "experimental,"<sup>209</sup> IRBs have approved protocols in which the consent forms inappropriately omit this and other essential information.<sup>210</sup> One court held the

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<sup>206</sup> In most jurisdictions, the unexcused violation of a relevant safety statute or regulation constitutes negligence per se. See, e.g., *Lowe v. Gen. Motors Corp.*, 624 F.2d 1373, 1380 (5th Cir. 1980). In some jurisdictions, violations of safety regulations create a rebuttable presumption or provide some evidence of negligence. See, e.g., *Sheridan v. United States*, 969 F.2d 72, 75 (4th Cir. 1992) (noting that under Maryland law, violation of statute or regulation is not negligence per se, but is only evidence of negligence); see also Paul Sherman, *Use of Federal Statutes in State Negligence Per Se Actions*, 13 WHITTIER L. REV. 831, 877-83 (1992) (providing an overview of different state approaches). In the context of FDA regulations governing the approval and marketing of prescription drugs and medical devices, for example, violations of the regulations may constitute negligence per se. See, e.g., *Stanton v. Astra Pharm. Prods., Inc.*, 718 F.2d 553, 565 (3d Cir. 1983); *Orthopedic Equip. Co. v. Eutsler*, 276 F.2d 455, 461 (4th Cir. 1960); *Toole v. Richardson-Merrell Inc.*, 60 Cal. Rptr. 398, 409 (Cal. Ct. App. 1967).

<sup>207</sup> See Robertson, *supra* note 148, at 531 (discussing the role of research regulations in defining an IRB standard of care against which courts may measure IRB conduct).

<sup>208</sup> See Sherman, Silverstein, Kohl, Rose & Podolsky, CLINICAL TRIALS LITIGATION, available at <http://www.sskrplaw.com/gene/> (last visited July 1, 2004) (providing links to complaints and other preliminary documents in a dozen pending or settled lawsuits alleging negligent research practices).

<sup>209</sup> 45 C.F.R. § 46.116(a) (2003).

<sup>210</sup> Johns Hopkins University's IRB approved research with a consent form lacking this information in the protocol that led to the death of Ellen Roche. The FDA inspected Johns Hopkins' Bayview Medical Center after her death in the hexamethonium study, and it reported that:

[t]he consent form failed to identify that research procedures involving inhalation of hexamethonium bromide were experimental. For example, the consent form provided that 'hexamethonium is a medication that has been used during surgery, as a part of anesthesia.' The subjects were not informed that hexamethonium bromide had never been approved to be administered by inhalation and that this route of administration was experimental.

FDA, FORM 483, FEI No. 1119912, INSPECTIONAL OBSERVATIONS 3 (Sept. 7, 2001), available at <http://www.fda.gov/ora/frequent/483s/bayviewirb483.html> (last visited July 1, 2004) [hereinafter FDA Hopkins Inspection Form]. The inspection form also noted that the IRB failed to follow appropriate full board review procedures in dealing with the research protocol as recommended by FDA guidelines on

NIH vicariously liable for the negligent failure of its employees to obtain informed consent and for negligent deviation from an IRB-approved protocol, both clear regulatory violations.<sup>211</sup> IRBs also have received warnings for violating the regulatory recusal provision by allowing members with interests in various studies under review to remain in the room and vote,<sup>212</sup> although a plaintiff might find it more difficult to prove a causal connection between non-compliance with this particular regulatory requirement and an injury that ultimately occurred.<sup>213</sup>

Even if the IRB conscientiously adheres to its regulatory mandate, it must depend to some degree on the care and candor of each researcher who conducts an approved protocol. Unfortunately, the IRB's trust sometimes appears to be misplaced. In one case, an investigator modified an IRB-approved informed consent form, deleting all references to the experimental nature of a device being used in an investigational eye surgery. The plaintiff was injured and sued, alleging that the surgeon and the IRB violated the federal research regulations dealing with informed consent.<sup>214</sup> Recognizing the IRB's responsibility for failing to monitor the investigator's compliance with informed consent and protocol requirements, the court concluded that, where the hospital undertakes the responsibility of informing patient-subjects of the experimental nature of their procedures and assumes the regulatory responsibility of monitoring the research as it proceeds, it is appropriate to hold the hospital as well as the physician-investigator liable in negligence for injuries arising from the lack of informed consent.<sup>215</sup> In a different case of intervening researcher misconduct, however, the court allowed the

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IRB operations. *See id.* (noting a “[f]ailure to review research at fully convened IRB meetings at which a majority of IRB members are present . . . [and that] [a]ll of the protocols, including protocol renewals, amendments, expedited reviews, and adverse events, approved by the subcommittee, are approved by a single block vote at the end of fully convened meetings of the IRB”). Other consent forms improperly omit information about risks of study procedures. *See Steinbrook, supra* note 11, at 629 (describing OHRP's criticism of IRBs supervising two large multi-center clinical trials for “approving informed-consent documents that inadequately described the purpose of the research, the nature of the experimental design, and the risks—most notably, death”).

<sup>211</sup> *Tivoli v. United States*, 1996 WL 1056005 (S.D.N.Y. 1996).

<sup>212</sup> 45 C.F.R. § 46.107(e); *see also* FDA Hopkins Inspection Form, *supra* note 210, at 4 (explaining that, during several meetings at which IRB members had conflicts of interest in studies under review, the minutes documented that the members abstained from voting, but there was no evidence of these abstentions on the audiotapes of the meetings).

<sup>213</sup> In the case of IRB liability, courts will require plaintiffs to prove a causal link between the alleged IRB negligence or non-compliance and the injury. Unless the court determines that the IRB's negligence was a substantial factor leading to the plaintiff's injury, it appears unlikely that a supervising IRB will be found legally responsible. *See* Robert J. Katerberg, *Institutional Review Boards, Research on Children, and Informed Consent of Parents: Walking the Tightrope Between Encouraging Vital Experimentation and Protecting Subjects' Rights*, 24 J.C. & U.L. 545, 574 (1998); *see also* Bordas, *supra* note 148, at 149.

<sup>214</sup> *Kus v. Sherman Hosp.*, 644 N.E.2d 1214, 1218 (Ill. App. Ct. 1995).

<sup>215</sup> *Id.* at 1218-21 (finding that, if the IRB had audited the investigator's medical records during the 1½ years prior to the plaintiff's experimental surgery, it would have discovered that the investigator was using a modified consent form that omitted the fact that the device was investigational).

defendant IRB to claim that it was unaware of, and thus unable to prevent, the researcher's negligent actions that ultimately caused the plaintiff's injuries.<sup>216</sup> IRBs are generally well aware, however, that investigators require supervision.

Once an IRB makes the judgment that the risks and benefits associated with proposed research are acceptable and approves a protocol, the researcher essentially promises to abide by the approved procedures. In another errant investigator case, a court denied a hospital's motion for summary judgment where the plaintiff was injured after undergoing laser eye surgery on both eyes, in violation of the approved protocol.<sup>217</sup> The opinion referred to the hospital and its IRB interchangeably in discussing potential liability for the plaintiff's injury. Under the assumption that the hospital owed the plaintiff a duty of care in the conduct of research protocols, the court noted deficiencies in the IRB's review, in particular the fact that the board appeared to have accepted without discussion the principal investigator's assurances that the risks of the single-eye experimental surgery were acceptable.<sup>218</sup> The court observed that, although the protocol clearly did not permit the inclusion of subjects with the plaintiff's type of eye problem, she underwent the operation anyway, "apparently under the auspices of the protocol" and that the departures from the protocol guidelines "could be seen as examples of negligent, or even reckless, conduct."<sup>219</sup> The regulations require each IRB to solicit reports of protocol deviations from investigators in order to facilitate the board's role as a research monitor,<sup>220</sup> but the court in this case appears willing to hold the IRB responsible for the negative outcome of protocol deviations even when the PI failed to report them.<sup>221</sup>

Some IRB members appear to be under the misguided impression that "following the rules" (for example, ensuring that every subject signs a consent form and receives a copy or that every ongoing protocol receives an annual review) protects the board from liability in the event that a research subject suffers an

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<sup>216</sup> *Hamby v. Univ. of Kentucky Med. Ctr.*, 844 S.W.2d 431, 435 (Ky. Ct. App. 1992) (finding that the jury had determined that the researcher's deviation from the protocol did not cause the plaintiff's injury, which rendered moot the question of the institution's independent negligence, and suggesting that it would be inappropriate to hold the medical center responsible unless there was evidence that the institution had actual knowledge of the protocol deviation); *see also* Bordas, *supra* note 148, at 149.

<sup>217</sup> *Gregg v. Kane*, 1997 U.S. Dist. LEXIS 14269 (E.D. Pa. 1997) (denying defendant hospital's motion for summary judgment). The protocol governing the experimental procedures prohibited operations on fellow eyes and on patients with a high degree of myopia. *Id.* at \*2-4.

<sup>218</sup> *Id.* at \*9 ("[N]either the IRB statement granting unconditional approval nor the minutes of IRB meetings discussing the protocol contain any indication that [an independent] risk assessment was done.").

<sup>219</sup> *Id.* at \*10. In discussing the allegations, the court also noted the IRB's responsibility for ensuring that research subjects give informed consent according to the standards set out in the federal regulations. *Id.* at \*11-12. After the subsequent trial, however, the jury found in favor of the hospital and its IRB. *Gregg v. Kane*, 1998 U.S. Dist. LEXIS 8437 (E.D. Pa. 1998).

<sup>220</sup> *See supra* notes 77-78 and accompanying text.

<sup>221</sup> *See Gregg*, 1997 U.S. Dist. LEXIS 14269, at \*10.

injury. Unlike some regulatory schemes designed to set out the optimal standard of care for a particular activity, the human subjects protection regulations were drafted in an open-ended fashion that not only invites but requires IRBs to exercise considerable judgment.<sup>222</sup> In other words, the regulations only set out minimum standards for the protection of humans who participate in research, and compliance with research regulations seldom should serve as conclusive evidence that an IRB has exercised due care.<sup>223</sup>

An IRB not only must act within the scope of existing regulatory guidance, it also must act reasonably under the circumstances. If the relevant regulations provide inadequate guidance on a particular question, the board must exercise its judgment in a non-negligent fashion.<sup>224</sup> Therefore, in some circumstances, despite an IRB's compliance with the minimal standards set out in the regulations, a court may conclude that a reasonable board would have taken additional protective measures under the circumstances. The examples that follow illustrate just a few of the many ways in which an IRB could commit "bioethical malpractice."

Because of the degree of judgment inherent in the review of new research protocols and the supervision of ongoing clinical trials, an injured research subject could argue that an IRB's decision to approve a protocol (or the supervision accorded it once approved) constituted an error in judgment, despite literal compliance with the federal regulations. In fact, attempts to comply with explicit regulatory requirements may lead an IRB astray. The Johns Hopkins IRB's characterization of benefit in the proposed lead abatement research protocol, as described in the *Grimes* decision, illustrates this type of error. In a scathing opinion, Maryland's highest court criticized the Hopkins IRB for suggesting that the investigators change the characterization of prospective benefit in the consent form to include a claim that all participants, including the healthy controls

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<sup>222</sup> In contrast, the regulations governing the approval and marketing of new pharmaceuticals represent an attempt to define the optimal safety standards for these products. See Noah, *supra* note 187, at 2152.

<sup>223</sup> See Noah, *supra* note 187 at 2151 ("Courts routinely note that government standards establish only 'minimum' requirements, which a jury can decide a reasonable person should have exceeded under the circumstances."). Courts usually treat government regulations as establishing only minimum requirements for conduct. See, e.g., *Ferebee v. Chevron Chem. Co.*, 736 F.2d 1529, 1543 (D.C. Cir. 1984) (explaining that "federal legislation has traditionally occupied a limited role as the floor of safe conduct"). Even in the context of more comprehensive regulatory schemes, however, compliance with regulations typically provides no defense. "[M]ost jurisdictions consider proof of compliance with an applicable government safety standard at best as some relevant evidence when assessing allegations that a product is defective or that the defendant's conduct was negligent." Noah, *supra* note 187, at 2151; see also *Wells v. Ortho Pharm. Corp.*, 788 F.2d 741, 746 (11th Cir. 1986); *Plenger v. Alza Corp.*, 13 Cal. Rptr. 2d 811, 819 n.7 (Ct. App. 1992); *Savina v. Sterling Drug*, 795 P.2d 915, 931 (Kan. 1990); *Feldman v. Lederle Labs.*, 625 A.2d 1066, 1070 (N.J. 1993). The FDA or HHS could issue a rule to preempt state common law claims, but they have not done so to date.

<sup>224</sup> See Noah, *supra* note 187, at 2151-52 (describing the development of the common law rule against recognizing a regulatory compliance defense to liability).

proposed in the protocol, would benefit from participation, in order to bring the study into compliance with federal regulations dealing with research on children.<sup>225</sup> The court concluded that the IRB's decision to approve the research protocol was negligent not only for its failure to comply with regulations, but also for its more general abdication of responsibility to review "the potential safety and the health hazard impact of a research project."<sup>226</sup>

Not surprisingly, much of the prior litigation dealing with injuries in research has included claims of negligent failure to obtain informed consent or related claims that the plaintiff did not realize that the treatment was investigational.<sup>227</sup> Other research injury claims allege that the subject was not informed of a particular

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<sup>225</sup> See *Grimes v. Kennedy-Krieger Inst.*, 782 A.2d 807, 844 (Md. 2001). The court criticized the IRB's efforts to bring the proposed research into compliance with these standards. *Id.* at 814. Where the risk of a pediatric research plan is greater than minimal, the regulations state that the anticipated benefit to the subjects must justify the risk and that "[t]he relation of the anticipated benefit to the risk [must be] at least as favorable to the subjects as that presented by available alternative approaches." 45 C.F.R. § 46.405(b) (2003). For research without anticipated therapeutic benefit to the pediatric subjects, the regulations permit approval only if the research plan meets the following criteria: (1) the research presents only a "minor" increase over minimal risk to the subjects; (2) the pediatric subjects would likely undergo the procedures involved in the research while receiving standard care for their condition; and (3) the interventions or procedures are likely to yield generalizable knowledge about the subject's disorder or condition that is vitally important. *Id.* at § 46.406. Remarkably, the consent form did not identify any risks associated with the study procedures.

<sup>226</sup> *Grimes*, 782 A.2d at 813 (discussing in detail the IRB's negligent review of the research, and chastising the board for "instead suggesting to the researchers a way to miscast the characteristics of the study in order to avoid the responsibility inherent in nontherapeutic research involving children"). See Complaint for Dawanna Robertson et al., *Robertson v. McGee*, (N.D. Okla. 2001) (No. 01-CV-60), available at 2002 WL 535045 (alleging that "[a]n IRB has the responsibility to review and approve all aspects of a human clinical trial including the design of the protocol, the qualifications of the investigator, the informed consent document, the selection process of participants, the balance of risks and benefits, and the conduct of the trial"). As one commentator has observed, the direct versus indirect benefit analysis in research protocols can pose real challenges for IRBs. See Hazel Glenn Beh, *The Role of Institutional Review Boards in Protecting Human Subjects: Are We Really Ready to Fix a Broken System?*, 26 LAW & PSYCHOL. REV. 1, 11-12 (2002). In the *Grimes* protocol, some children benefited directly from study interventions, while others only stood to benefit indirectly, if at all. Children who were already occupying lead-contaminated housing that underwent abatement pursuant to the protocol arguably received a more direct benefit than those in control groups whose homes underwent no repair. All children received the benefit of blood lead-level monitoring, but this benefit resulted from inclusion in the study rather than directly from the studied intervention (the lead abatement strategies). See *id.* The federal regulations do not provide detailed guidance to IRBs in assessing prospective benefit, and, not surprisingly, many IRBs find it difficult to identify which procedures offer the prospect of direct as opposed to indirect benefit. Nevertheless, this distinction is critical because IRBs should refrain from "justifying the risks of procedures that are designed solely to answer the research questions based on the likelihood that another procedure in the protocol is likely to provide a benefit." *Id.* at 12 (citing NAT'L BIOETHICS ADVISORY COMM'N, ETHICAL AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS 77 (2001)).

<sup>227</sup> See, e.g., *Karp v. Cooley*, 493 F.2d 408 (5th Cir. 1974); *Sexton v. United States*, 644 F. Supp. 755 (D.D.C. 1986), *aff'd*, 832 F.2d 629 (D.C. Cir. 1987); *Mink v. Univ. of Chicago*, 460 F. Supp. 713, 717 (N.D. Ill. 1978), *aff'd*, 727 F.2d 1112 (7th Cir. 1984); *Gaston v. Hunter*, 588 P.2d 326, 350 (Ariz. Ct. App. 1978); *Estrada v. Jacques*, 321 S.E.2d 240, 254 (N.C. Ct. App. 1984).

risk, which then materialized and caused harm. The informed consent regulations contain a variety of explicit requirements that IRBs generally enforce by evaluating a sample consent form, but the actual consent process offers ample opportunity for negligence by the researcher, unless carefully monitored by the board. As explained above, the regulations require investigators to provide a wide range of information to research subjects,<sup>228</sup> and to ensure that the research subject understands the information and has an opportunity to ask questions,<sup>229</sup> but the existing consent process may prove inadequate in the research context.<sup>230</sup>

No one would suggest that the regulations preclude IRBs from requiring investigators to provide additional information, or to ensure by other means in other ways, in addition to the written consent form, that the research subjects genuinely understand the risks and benefits of participation in a particular trial. A court might conclude, on this basis, that an IRB has failed in its duty to protect research subjects when it approves a protocol with a consent form and procedure that is incomplete, given the risks of procedures for the particular protocol, or when it fails to adequately supervise adequately the investigator's compliance with informed consent requirements due to a lack of resources or lack of concern, or when it fails to impose additional consent safeguards when a particular trial (or population of prospective subjects) appears to demand it.<sup>231</sup>

As a practical matter, IRBs certainly have the resources and the clout to insist on additional information in the consent form, but boards will find it more difficult to monitor how this information gets transmitted to prospective research participants. The therapeutic misconception provides an example of a problematic situation in which an IRB may lack control over the consent process. Because prospective subjects may fail to appreciate the non-therapeutic nature of much research and instead may enroll in research expecting medical benefit, the IRB has an obligation to correct such common misimpressions by ensuring that the informed consent process accurately describes the potential for individual benefit so that patients can make a meaningful decision about participation.

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<sup>228</sup> See *supra* notes 57-61 and accompanying text.

<sup>229</sup> See 45 C.F.R. § 46.116 (2003) (requiring that the investigator seek consent "only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate").

<sup>230</sup> See Epstein, *supra* note 166, at 1155 (explaining that "the doctrine of informed consent is under far greater pressure [in the research context], first, because of the persistent conflicts of interest between the physician's experiment and the patient's well-being, and, second, greater uncertainty means that there is much more that should be said about the problems").

<sup>231</sup> In discussing informed consent standards in the research context, some courts and commentators have argued that certain factors unique to the research setting, including greater uncertainty about the risks and therapeutic benefit of experimental interventions, and concerns about conflicts of interest, support heightened consent requirements compared with the customary approach in standard medical care. See Noah, *supra* note 56, at 370-71 (concluding, however, that the research context does not differ significantly enough from the standard treatment context to justify radically different requirements for consent).

Unfortunately, written explanations alone may prove unavailing, but resource constraints mean that the board may have little option but to focus on the completeness and readability of the consent form, leaving the investigators to ensure that participants actually understand the speculative prospect, if any, of therapeutic benefit.

The regulations also leave to researchers and IRBs the task of making judgments about complex scientific matters with significant ethical implications, such as trial design.<sup>232</sup> The randomized controlled trial (RCT) represents the “gold standard” of clinical investigation.<sup>233</sup> In general, new drugs and therapies undergo three phases of clinical testing after the completion of *in vitro* and animal studies. In the case of novel therapies, investigators may require several Phase II studies to evaluate technical feasibility questions, in addition to efficacy, before proceeding to Phase III trials that actually test the efficacy of investigational therapies in larger numbers of subjects who suffer from the targeted medical condition.<sup>234</sup>

The promise of novel, useful scientific information provides part of the justification for subjecting trial participants to the risks of experimental therapies. How, then, should IRBs assess the ethical merits of these rigorous, hypothesis-testing investigations compared to observational or pilot studies which do not necessarily demonstrate efficacy but instead generate hypotheses and may uncover

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<sup>232</sup> See Antman et al., *supra* note 55, at 762. Clinical trial design has increased significantly in the degree of complexity in recent years, often employing multiple arms and studying numerous and sometimes surrogate endpoints. See Michael S. Lauer & Eric J. Topol, *Clinical Trials—Multiple Treatments, Multiple End Points, and Multiple Lessons*, 289 JAMA 2575, 2576 (2003). More complex study designs pose additional challenges in data analysis, and IRBs should consider these issues in evaluating the potential usefulness and reliability of the data.

<sup>233</sup> Ulrich Abel & Armin Koch, *The Role of Randomization in Clinical Studies: Myths and Beliefs*, 52 J. CLINICAL EPIDEMIOLOGY 487, 487 (1999); see also Stuart J. Pocock & Diana R. Elbourne, *Randomized Trials or Observational Tribulations?*, 342 NEW ENG. J. MED. 1907, 1907-08 (2000) (advocating continued emphasis on RCTs, in part because in observational studies the treatment is selected for the particular patient and this selection bias may create cumulative outcome differences that are not a result of the treatment itself). *But see* Kjell Benson & Arthur J. Hartz, *A Comparison of Observational Studies and Randomized, Controlled Trials*, 342 NEW ENG. J. MED. 1878 (2000) (concluding that observational studies and RCTs were equally useful in accurately assessing the treatment effects of a wide variety of therapies); John Concato et al., *Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs*, 342 NEW ENG. J. MED. 1887, 1890-91 (2000).

<sup>234</sup> See LARS NOAH & BARBARA A. NOAH, LAW, MEDICINE, AND MEDICAL TECHNOLOGY: CASES AND MATERIALS 137-52 (2002) (discussing the various phases of drug development). In Phase I, a small number of healthy volunteers participate in a study to measure toxicity and to determine appropriate dosing. In Phase II, a somewhat larger number of individuals with the targeted disease or condition test the drug for efficacy and risks associated with its use. Finally, in Phase III, a large population of individuals with the targeted disease, along with a control group of some sort, test the product's safety and efficacy. *Id.* at 145-46.

side-effects?<sup>235</sup> Scientists continue to debate whether poorly designed clinical trials can still generate useful scientific information,<sup>236</sup> and IRBs must make difficult tradeoffs between rigorously designed RCTs and ethical concerns about patient protection.<sup>237</sup> Boards may find that consideration of these sorts of trial design distinctions further complicates the already formidable task of weighing risk and benefit to subjects, yet a court could conclude that failure to do so constitutes negligence.

For this reason, even when early studies successfully resolve questions of appropriate research procedure and support assertions of safety and therapeutic efficacy, the IRB should evaluate the proposed design of any follow-up trials in order to determine whether they can produce useful data.<sup>238</sup> IRBs should include in their preliminary review a careful evaluation of study design issues, such as statistical power, in deciding whether to approve proposed research protocols, recognizing that it may be inappropriate to subject study participants to the risks of research in underpowered or otherwise poorly-designed trials.<sup>239</sup> Many IRBs probably fail to consider these questions; even those IRBs that choose to tackle such complex biostatistical questions still may struggle to make rational, consistent

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<sup>235</sup> Similarly, the FDA sometimes authorizes so-called "Treatment INDs," which involve an open protocol or compassionate use of an investigational product, subject to IRB supervision, in part because of their hypothesis-generating value. *Id.* at 194-95.

<sup>236</sup> See Scott D. Halpern et al., *The Continuing Unethical Conduct of Underpowered Clinical Trials*, 288 JAMA 358, 359-60 (2002); see also Benjamin Freedman & Stanley H. Shapiro, *Ethics and Statistics in Clinical Research: Towards a More Comprehensive Examination*, 42 J. STAT. PLANNING & INFERENCE 233 (1994) (evaluating issues of research ethics including the basis for a study's estimation of sample size and its adoption of eligibility criteria that may compromise the effectiveness of human subject's research); Noah, *supra* note 56, at 400-02. On the other hand, even an RCT that enrolls insufficient numbers of patients to produce statistically significant results, or that lacks adequate controls, may nevertheless generate useful hypotheses, especially concerning safety information.

<sup>237</sup> Apart from the placebo controls debate, researchers also struggle with the question of whether and when to unblind double-blinded trials based on unpromising preliminary data.

<sup>238</sup> See Antman et al., *supra* note 55, at 762 (discussing problems with, and risks of, a small-enrollment RCT of neuronal transplantation surgery for Parkinson's disease patients that failed to demonstrate a statistically significant difference between those patients who were randomized to the surgery arm of the protocol and the controls). Poorly designed trials, even if not inherently risky, are only ethically justified if they will produce scientifically valid data, and courts have occasionally expressed a willingness to second-guess the FDA's approval of a product based on study design concerns. In one drug design defect case, the court allowed a jury to conclude, based on expert testimony, that the FDA erred in approving a drug based on methodologically-flawed clinical trials. See, e.g., *Tobin v. Astra Pharm. Prods., Inc.*, 993 F.2d 528 (6th Cir. 1993).

<sup>239</sup> See Halpern et al., *supra* note 236 (concluding that arguments in support of underpowered trials are flawed in most cases, and describing two limited situations in which underpowered research may be ethically appropriate). Sometimes the lack of sufficient statistical power results from inadequate funding to enroll and follow sufficient patients to produce a definitive result. See Antman et al., *supra* note 55, at 762-63. At least one pending lawsuit alleges that the IRB was negligent in approving the design of the study in which the plaintiff was injured. See *Complaint, Guckin v. Nagle*, 2002 WL 32151766 (Pa. Ct. Com. Pl. 2002) (No. 001425), available at 2002 WL 32151766 (naming as defendants the PI, hospital, IRB members, and medical device manufacturer).

decisions, particularly when those boards lack members with relevant expertise. It remains to be seen whether a court would ever go so far as to recognize a claim that a plaintiff injured in a statistically underpowered trial should never have been subjected to the risk of participation in such a study.

As explained above, IRBs also have an ethical and regulatory obligation to refuse approval of research that poses an inappropriate level of risk to human participants, but making such judgments can present a difficult challenge in some circumstances. In evaluating proposals for therapeutic research, the IRB must ensure that the study in fact has sufficient prospect of direct benefit to patient-subjects to justify its risks.<sup>240</sup> The regulations create two categories of risk—"no more than minimal risk" and "greater than minimal risk."<sup>241</sup> Different IRBs may disagree at a basic level about what sorts of interventions belong in one or the other of these categories. The regulations do not provide a laundry list of which interventions present no more than a minimal risk. Moreover, as one commentator has observed, the "research regulations do not clearly describe . . . how to balance the risks against the potential benefits for the subjects and against the knowledge the research may produce."<sup>242</sup>

Overburdened, undertrained IRBs tend to focus the bulk of their initial review efforts on matters of consent, giving short shrift to the risk-benefit calculus. A more structured approach to the analysis of prospective benefit than described in the regulations may assist IRBs in making the risk-benefit call.<sup>243</sup> Although the researcher's protocol may settle an important scientific question, the very nature of research suggests that participation in such a protocol may not be the best way to advance a participant's medical interests. In one recent trial comparing fluid management approaches for intensive care patients with acute respiratory distress syndrome, the OHRP halted the trial because of concerns that patients in one arm were not receiving the best current standard care. Despite the fact that the NIH-funded study had undergone multiple levels of review that raised concern about the study's scientific design, the study was allowed to proceed until the OHRP

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<sup>240</sup> Nancy M.P. King, *Defining and Describing Benefit Appropriately in Clinical Trials*, 28 J.L. MED. & ETHICS 332, 333 (2000).

<sup>241</sup> 45 C.F.R. § 46.102(i) (2003) (defining "minimal risk"). See also *supra* notes 49-56 and accompanying text (discussing IRB risk-benefit balancing).

<sup>242</sup> Jason H.T. Karlawish, *Research Involving Cognitively Impaired Adults*, 348 NEW ENG. J. MED. 1389, 1390 (2003) (describing a study comparing two different ventilator tidal volumes in which each alternative involved serious risks to the subject and both alternatives posed greater than minimal risks, and explaining that, although participation in the trial offered prospective benefits, it would be difficult for an IRB to assess which risks were justified by those benefits because the research also included procedures that were not intended to provide any benefit to study participants).

<sup>243</sup> See King, *supra* note 240, at 332-33 (suggesting that IRBs categorize benefit into "direct" benefit (actually arising from the treatment under study), "collateral" benefit (from being a research subject even if one does not receive the experimental treatment, including the benefit of regular medical examinations), and "aspirational" benefit (to society or future patients)).

intervened.<sup>244</sup> These sorts of scenarios can open the door to claims of negligent IRB judgment.

Even if a research subject receives unambiguous and complete information about the risks of participation, the subject may later allege, with the benefit of hindsight, that the risks of participation were too high. Particularly in the case of non-therapeutic research, an injured subject may attempt to argue that the IRB should never have provided him or her with the opportunity to take such a risk. In the context of non-therapeutic research, however, courts have recognized that where a subject voluntarily and knowingly chooses to participate, the defendant may argue assumption of risk.<sup>245</sup> In *Whitlock v. Duke University*, for example, a plaintiff claimed to have suffered organic brain injury in a simulated deep-dive research protocol.<sup>246</sup> The court dismissed the plaintiff's negligent failure to warn claims, noting that the plaintiff had sought out the opportunity to participate in the dive experiments in order to further his career and that the consent form included a warning about both known and unknown risks.<sup>247</sup> Nevertheless, one can imagine a non-therapeutic research protocol that so egregiously risks harm to participants that courts would choose not to allow an assumption of risk defense on the part of either the researcher or the board.<sup>248</sup>

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<sup>244</sup> Jeffrey M. Drazen, *Controlling Research Trials*, 348 NEW ENG. J. MED. 1377, 1377-79 (2003) (arguing, however, that in the case of NIH-sponsored trials, OHRP should limit its role to inappropriate conduct of approved trials and leave study design questions to NIH). Where the research objective improperly compromises the prospective subjects' best interests, courts implicitly have recognized that this type of ethical conflict of interest can justify an action in battery against a hospital. See *Mink v. Univ. of Chicago*, 460 F. Supp. 713, 716-18 (N.D. Ill. 1978) (describing the experimental administration of DES to pregnant women without their knowledge or consent, and allowing a battery claim against the hospital), *aff'd* 727 F.2d 1112 (7th Cir. 1984); see also Richard S. Saver, *Critical Care Research and Informed Consent*, 75 N.C. L. REV. 205, 226 & n.72 (1996) (discussing the implications of the *Mink* decision).

<sup>245</sup> In some routine medical malpractice cases, courts also have recognized assumption of risk as a valid defense. See, e.g., *Boyle v. Revici*, 961 F.2d 1060, 1063 (2d Cir. 1992) (concluding that a patient "may expressly assume the risk of malpractice and dissolve the physician's duty to treat a patient according to the medical community's accepted standards"); *Schneider v. Revici*, 817 F.2d 987, 995-96 (2d Cir. 1987) (allowing an express assumption of risk defense, and explaining that there is "no reason why a patient should not be allowed to make an informed decision to go outside currently approved medical methods in search of an unconventional treatment").

<sup>246</sup> *Whitlock v. Duke University*, 637 F. Supp. 1463, 1466 (M.D.N.C. 1986), *aff'd*, 829 F.2d 1340 (4th Cir. 1987); see also *Vodopost v. MacGregor*, 913 P.2d 779, 786-87 (Wash. 1996) (allowing plaintiff's negligent informed consent claim to proceed, and refusing to enforce an exculpatory clause contained in the consent form, where plaintiff suffered injuries in a high altitude breathing experiment).

<sup>247</sup> See *Whitlock*, 637 F. Supp. at 1467-68; cf. *Karp v. Cooley*, 349 F. Supp. 827, 835 (S.D. Tex. 1972) (explaining that the consent form dealing with the implantation of an artificial heart contained detailed information of risks, and directing a verdict for the surgeon on the issue of informed consent), *aff'd*, 493 F.2d 408, 419-23 (5th Cir. 1974).

<sup>248</sup> For example, one could argue that the hexamethonium inhalation experiments at Johns Hopkins University should never have received approval and that the plaintiff's consent in the case was immaterial given the non-therapeutic nature of the research and the serious, knowable risks of injury to participants. See *supra* notes 49-56 and accompanying text.

Ideally, IRBs also ought to consider how the source and amount of the study's funding and the intended use of the study's data affect questions of its scientific merit. Industry-funded studies designed to obtain marketing permission from the FDA for an additional medical indication, or to justify claims of equality or superiority to a competitor product, deserve careful scrutiny in order to determine whether the trial design is scientifically sound and whether it is ethically appropriate to expose human subjects to the risks of participation.<sup>249</sup> For instance, in 1999, Bristol-Myers Squibb designed and funded a clinical trial (with the rather optimistic acronym "PROVE IT") to demonstrate that, although Lipitor® (atorvastatin calcium) lowers cholesterol more than Pravachol® (prevastatin), the two products are equally effective in preventing heart attack and death. Critics of the study argued that the study lacked the statistical power—both in numbers of patients enrolled and in length of enrollment—to discover real differences in clinical endpoints between the two products, and that the industry sponsor deliberately designed it this way.<sup>250</sup> Research subjects who suffer injury in such a study might successfully claim that the supervising board ought never to have subjected them to the risks of participation, including an unnecessary risk of disease exacerbation or adverse events.<sup>251</sup>

Where there is genuine controversy over an ethical question, one IRB may decide to permit a research plan that a different board would view as unapprovable, and this sort of judgment could open the door to a judicial determination of negligence. For example, the clinical research community has hotly debated the ethics of placebo controls in clinical trials.<sup>252</sup> When a researcher designs a trial to test the relative effectiveness and safety of two different treatments for the same

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<sup>249</sup> See Franklin G. Miller & Andrew F. Shorr, *Ethical Assessment of Industry-Sponsored Clinical Trials: A Case Analysis*, 121 CHEST 1337, 1338-39 (2002) (providing an example of a placebo-controlled study that was apparently "designed to showcase the sponsor's newer drug"); see also Bodenheimer, *supra* note 119, at 1541 (discussing the myriad ways in which industry sponsors can design clinical trials to produce desired results); Sheryl Gay Stolberg & Jeff Gerth, *Drug Makers Design Studies with Eye to Competitive Edge*, N.Y. TIMES, Dec. 23, 2000, at A1.

<sup>250</sup> See Stolberg & Gerth, *supra* note 249 (quoting one critic who opined that "[t]he PROVE IT trial is a particularly extreme example of a study designed purely for marketing, rather than scientific purposes"); see also Gina Kolata, *Study of Two Cholesterol Drugs Finds One Halts Heart Disease*, N.Y. TIMES, Nov. 13, 2003, at A1 (describing study results that demonstrated Lipitor's superior effectiveness in halting atherosclerosis; in response, the competitor product's manufacturer pointed out that the study failed to demonstrate improved clinical outcomes in patients taking Lipitor).

<sup>251</sup> See Miller & Shorr, *supra* note 249, at 1341.

<sup>252</sup> See generally Ezekiel J. Emanuel & Franklin G. Miller, *The Ethics of Placebo-Controlled Trials – A Middle Ground*, 345 NEW ENG. J. MED. 915 (2001) (arguing that placebo-controlled trials are permissible when proven therapies exist but only if certain ethical and methodologic criteria are met); Benjamin Freedman et al., *Placebo Orthodoxy in Clinical Research II: Ethical, Legal, and Regulatory Myths*, 24 J.L. MED. & ETHICS 252 (1996) (challenging a number of common beliefs concerning the value of placebo controls); Sharona Hoffman, *The Use of Placebos in Clinical Trials: Responsible Research or Unethical Practice?*, 33 CONN. L. REV. 449 (2001) (describing and discussing the competing arguments).

condition, the genuine uncertainty as to the relative merits of the two treatments is known as “equipoise.”<sup>253</sup> Commentators have noted that equipoise is an ethical necessity in order to justify the risks to human subjects in clinical research of this kind.<sup>254</sup> Unfortunately, a trial comparing an active experimental medication to a placebo, while providing equipoise, may unnecessarily deprive those participants who are randomized to the placebo of active therapy, increasing the risk that their condition will worsen.<sup>255</sup> To further complicate the debate, placebo controls generally permit the gathering of statistically significant data using fewer human participants overall (thereby subjecting fewer individuals to the risks of the research). Nevertheless, many ethicists agree that placebo-controlled studies are only appropriate when evaluating drugs or other interventions to treat conditions for which there is no known effective treatment.<sup>256</sup>

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<sup>253</sup> Benjamin Djulbegovic & Mike Clarke, *Scientific and Ethical Issues in Equivalence Trials*, 285 JAMA 1206, 1206 (2001) (describing the varying degrees of scientific uncertainty or equipoise).

<sup>254</sup> Benjamin Freedman, *Equipoise and the Ethics of Clinical Research*, 317 NEW ENG. J. MED. 141, 141 (1987); see also Don Marquis, *How to Resolve an Ethical Dilemma Concerning Randomized Clinical Trials*, 341 NEW ENG. J. MED. 691 (1999) (describing the conflict that physicians experience when recommending that their patients enroll in randomized, placebo-controlled clinical trials); Stuart L. Nightingale, *Challenges in Human Subject Protection*, 50 FOOD & DRUG L.J. 493, 498-99 (1995).

<sup>255</sup> Of course, this ethical argument assumes that active therapy is always better than placebo, but this assumption is not necessarily correct. Theoretically, the active agent being tested may prove to be so toxic that the placebo group is relieved to have been randomized into that arm. More generally, experts have recognized that subjects enrolled in clinical trials apparently achieve better outcomes than patients with the same condition who receive treatment from physicians, whether they receive the experimental treatment or a placebo control. See John D. Lantos, Editorial, *The ‘Inclusion Benefit’ in Clinical Trials*, 134 J. PEDIATRICS 130, 130 (1999) (“A number of explanations have been offered for the apparent benefit of RCT participation, including selection bias, placebo effects, and adherence to well-defined protocols [for other aspects of disease management].”). At other times, placebos may prove to be as efficacious as active therapy. See Shankar Vedantam, *Against Depression, a Sugar Pill Is Hard to Beat*, WASH. POST, May 7, 2002, at A1 (describing a recent analysis of 96 antidepressant clinical trials that concluded that placebos worked as well as the study drug in a majority of the trials surveyed). In one recent trial, the herbal remedy St. John’s Wort worked for 24% of depressed patients in the study, while the prescription drug Zoloft® proved efficacious for 25% of patients, but the placebo worked for a whopping 32%. *Id.* But see John C. Bailar, *The Powerful Placebo and the Wizard of Oz*, 344 NEW ENG. J. MED. 1630 (2001) (reporting on several studies which found little evidence that placebos had powerful clinical effects); Asbjorn Hrobjartsson & Peter C. Gotzsche, *Is the Placebo Powerless? An Analysis of Clinical Trials Comparing Placebo with No Treatment*, 344 NEW ENG. J. MED. 1594 (2001) (concluding that placebos generally had little effect, though they produced possible benefits for the treatment of pain).

<sup>256</sup> Miller & Shorr, *supra* note 249, at 1339 (noting that placebo controls also might be ethically appropriate in trials dealing with conditions known to have high rates of placebo response). Although the term “placebo” usually refers to an inert substance used in comparison with an active medication, placebo controls are not limited to drug trials. Some IRBs have approved research involving placebo or “sham” surgery, which has prompted sharp debate in the biomedical community. See, e.g., Thomas B. Freeman et al., *Use of Placebo Surgery in Controlled Trials of a Cellular-Based Therapy for Parkinson’s Disease*, 341 NEW ENG. J. MED. 988 (1999); Sam Horng & Franklin G. Miller, *Is Placebo Surgery Unethical?*, 347 NEW ENG. J. MED. 137 (2002) (discussing a placebo-controlled trial of arthroscopic knee surgery, and addressing the competing arguments more generally); Ruth Macklin, *The Ethical Problems with Sham Surgery in Clinical Research*, 341 NEW ENG. J. MED. 992 (1999).

In contrast, when effective alternatives to the studied therapy exist, even for treating a relatively mild medical condition, ethicists (and many IRB members) argue that placebo-controlled studies subject participants to unnecessary and avoidable risks.<sup>257</sup> Although the arguments in favor of limiting the use of placebo controls appear compelling, pharmaceutical manufacturers continue to push for their use because placebos often permit a clearer assessment of the studied drug's safety and efficacy,<sup>258</sup> which is essential for obtaining premarket approval from the FDA.<sup>259</sup> IRBs must take care to avoid allowing these sorts of influences to distort their evaluation of study design questions.

Nevertheless, under existing regulations, IRBs may choose to approve placebo-controlled studies in some circumstances, as long as the risks to subjects are minimized "[b]y using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk."<sup>260</sup> Where the only available active control is not particularly effective, or where the underlying disease is not life-threatening, some boards may conclude that a placebo control is ethically permissible in order to yield statistically valid results. In other cases, an

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<sup>257</sup> Miller & Shorr, *supra* note 249, at 1339 (explaining that a placebo controlled trial of an asthma study would be ethically inappropriate, not only because the placebo response for asthma therapies is low, but also because such trials would involve withdrawing asthma patients from highly effective standard therapies such as inhaled corticosteroids, which can exacerbate symptoms); see also C. Michael Stein & Theodore Pincus, *Placebo-Controlled Studies in Rheumatoid Arthritis: Ethical Issues*, 353 LANCET 400, 400-01 (1999) (explaining that placebo controls in trials designed to study therapies for chronic diseases like rheumatoid arthritis and hypertension may place subjects at risk of poor disease control and irreversible damage). The recently revised Declaration of Helsinki takes the position that placebo controls are never ethically appropriate where an efficacious therapy is known to exist, though the question remains subject to debate. See Susan Okie, *Health Officials Debate Ethics of Placebo Use*, WASH. POST, Nov. 24, 2000, at A3 (noting that no one defends placebo controls where established therapies exist to treat serious and measurable conditions such as infections, diabetes and cancer); see also Timothy S. Jost, *The Globalization of Health Law: The Case of Permissibility of Placebo-Based Research*, 26 AM. J.L. & MED. 175 (2000) (evaluating the negative effect of the globalization of health law on placebo-controlled human subjects research); David J. Kupfer & Ellen Frank, *Placebo in Clinical Trials for Depression: Complexity and Necessity*, 287 JAMA 1853 (2002) (examining results from two studies on the use of placebo-controlled clinical trials for major depression, and noting the extensive problems with such trials); Robert Temple & Susan S. Ellenberg, *Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments: Ethical and Scientific Issues*, 133 ANNALS INTERNAL MED. 455 (2000) (concluding that the acceptability of placebo-controlled trials should be determined by whether the patient will be harmed by deferral of therapy).

<sup>258</sup> AMA, COUNCIL ON ETHICAL & JUDICIAL AFF., CODE OF MEDICAL ETHICS: THE USE OF PLACEBO CONTROLS IN CLINICAL TRIALS, OPINION No. E-2.075 (1996), available at <http://www.ama-assn.org/ama/pub/category/8424.html> (last updated June 22, 2002).

<sup>259</sup> See NOAH & NOAH, *supra* note 234, at 159. The FDA agrees with this argument, recognizing that placebo controls are only appropriate where no efficacious standard therapy exists. 53 Fed. Reg. 41,516, 41,519-21 (1988). The agency's regulations require, however, that investigators design trials to generate valid scientific results. 21 C.F.R. §§ 56.111(a)(2), 312.22(a) (2003).

<sup>260</sup> 45 C.F.R. § 46.111(a)(1) (2003). Many IRBs ask researchers to provide an ethical, as opposed to a scientific, reason for using a placebo control. Researchers frequently fail to appreciate the ethical concerns surrounding placebo use and focus instead on the scientific desirability of placebo-controlled trials.

IRB might decide, quite rationally, to approve a placebo-controlled study because comparison of a study drug against an active control may not yield statistically significant data where the differences in the mode of action between the study drug and the only available active control are very subtle. Such a judgment still puts an IRB at risk of liability, however; the regulations do not expressly forbid placebo controls, but a court could disagree with a board's judgment in a particular case.

Consider this intriguing, though never-litigated, example of potential "bioethical malpractice" by an IRB. Suppose an investigator proposes to conduct a double-blind RCT of a new drug for hypertension. According to her proposed protocol, half of the patients will be randomized to the experimental study medication; one-quarter to an approved medication for hypertension (the "active control"); and one-quarter to a placebo. The introductory section of the informed consent form explains to participants that the purpose of the study is to evaluate a new, apparently safer and more effective therapy for hypertension. The consent form also explains in the "procedures" section that one-quarter of the patients will receive a placebo (and that a placebo is "like a sugar pill"), and the form mentions that one risk of participation is "worsening hypertension if the experimental medication does not work for you."

After analyzing the study results from the first two months, the PI suspects, based on the benefits and side effects that the patients experience, that the study medication works significantly more safely and effectively than the standard medication. She also notices that many of the participants who were randomized to the placebo arm now have uncontrolled hypertension. The study sponsor, a large pharmaceutical company, provided her with funding to conduct the study for six months and it wants the full six months' worth of data in order to maximize its chances of receiving marketing permission from the FDA. She wonders whether she should notify the IRB or halt the research. Should the IRB have approved this study in the first place? If a study participant in the placebo arm suffers a stroke as a result of uncontrolled blood pressure, should the IRB face tort liability? Most IRBs probably would have corrected the flawed consent, and most probably would have expressed concern about the use of a placebo arm in these circumstances, but how many IRBs would have anticipated the questions posed by the interim data?

To date, no research subject has sued an IRB or clinical investigator for approving or conducting a trial with an inappropriate placebo control. Theoretically, however, a subject could sue an IRB, claiming that, although the investigator fully informed him or her of the risks of participating in a placebo-controlled clinical trial, the board was negligent in approving the protocol as designed. A plaintiff randomized into the placebo arm of the study whose disease progressed while receiving no active treatment could argue that the study design was flawed, despite the fact that the regulations permit placebo-controlled clinical trials. On the other hand, a patient who suffers an injury while participating in a study comparing an experimental agent to an active control might allege that the

IRB was negligent in approving a study design that lacks scientific utility because it is unlikely to produce statistically significant differences between the two test articles and that, therefore, the risks of performing the research were unacceptable.

An injured research subject also might assert that an IRB was negligent in failing to provide continuing review of the research on a semi-annual or quarterly basis rather than annually, if the protocol presents unusual risks requiring closer supervision.<sup>261</sup> To the extent that an IRB relies on the extra supervision of a DSMB in initially approving a protocol, but fails to follow up with the committee or fails to process adverse event reports promptly, the IRB may be liable in negligence for the results of its lax oversight.<sup>262</sup> The IRB's duty to monitor ongoing research clearly includes the need to make judgments about when to stop a protocol if interim data suggest previously unforeseen risks. Interim data analysis improves the safety of this type of research, and IRBs must respond quickly to emerging information in order to avoid exposing new enrollees to unnecessary risks.<sup>263</sup> IRBs, relying on their own interim review or reports from a DSMB, must balance concerns about unnecessary exposure to risk (if the trial is halted "too late") against prematurely abandoning promising research in cases where early adverse events turn out to be random statistical variations.<sup>264</sup>

One recent example of a controversy involving data monitoring and the decision to halt an ongoing clinical trial for safety reasons may prove instructive.<sup>265</sup>

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<sup>261</sup> Recall that the federal regulations require annual review at a minimum, but certainly permit more frequent reconsideration of an active protocol. See 45 C.F.R. § 46.109(e) (2003); *supra* notes 76-97 and accompanying text (discussing regulatory requirements for continuing review).

<sup>262</sup> Cf. Herson, *supra* note 80, at 557-58 (suggesting that DSMBs also face potential liability for "errors and omissions in the decisions/recommendations they make during the course of the clinical trial").

<sup>263</sup> Kyra J. Becker & David L. Tirschwell, *Ensuring Patient Safety in Clinical Trials for Treatment of Acute Stroke*, 286 JAMA 2718, 2718 (2001) (explaining that, in one large trial, 328 additional patients enrolled during the time it took to complete interim analysis of data on the first 300 enrollees).

<sup>264</sup> *Id.* at 2718. Although the ostensible third party beneficiaries of research to develop a new treatment would not have standing to complain that an IRB caused them injury by refusing to approve research supporting the licensing of the treatment, it is easier to imagine claims that an IRB was negligent in approving research in which the prospective benefit to participants did not justify the risks.

<sup>265</sup> Occasionally, study sponsors also will call a halt to ongoing research for financial reasons. In a large, randomized, double-blind study to compare a new formulation of a calcium channel blocker with standard therapies for hypertension, the data failed to demonstrate equivalence between the therapies after accruing 32% of the target data. The sponsor opted to terminate the trial two years early because of "business considerations." See Bruce M. Psaty & Drummond Rennie, *Stopping Medical Research to Save Money: A Broken Pact with Researchers and Patients*, 289 JAMA 2128 (2003) (also describing other examples of research halted for commercial reasons alone).

Human subjects committee approval of the protocol is predicated on a sample size and length of follow-up adequate to test the study's hypothesis. . . . The participants in [the study] were not only deprived of personal benefit from the completed trial, but also the social benefit of genuine scientific contributions from an adequately powered study. . . . What the company apparently treated as a simple commercial matter rendered the original promise to participate

The so-called “super aspirin” trials were a series of studies designed to evaluate the effectiveness of a new class of anti-clotting drugs in preventing heart attacks and strokes. The sponsoring companies hoped that these very expensive drugs would prove significantly more effective than aspirin in preventing blood clots and their associated adverse health effects. In five large studies testing four slightly different versions of the drug, the study participants taking super aspirin experienced significantly higher death rates.<sup>266</sup> In the fifth study, which enrolled 9,200 patients around the world, the death rate for enrollees taking the study medication was notably higher than that of subjects taking the placebo.<sup>267</sup> Each of the previous four trials had produced similar conclusions—the combined data from the five trials demonstrated that super aspirin not only failed to prevent death among patients with heart disease but actually increased the risk of death by thirty-six percent.<sup>268</sup>

Given that the data from the four previous studies suggested serious problems with this class of medications, should the IRB even have approved the fifth study? Each successive research proposal should include all of the data from the preceding studies, so at what point should the reviewing IRB have refused to approve further research? A participant in the fifth study, randomized to the super-aspirin arm before suffering a cardiac arrest, reasonably might argue that the supervising IRB was negligent in allowing the research to proceed, or should have included in the informed consent form specific information about the increased death rates of study participants in the preceding trials. Technically, each of the studies employed a slightly different chemical entity from the same class of drugs, so a researcher might argue that data from a prior study are not relevant to studies that follow, but a reasonable interpretation of the informed consent regulations suggests that disclosure of prior related study results is ethically and legally required in cases like these.

These sorts of situations recur with disturbing regularity. In 2001, the sponsors and an independent DSMB suspended another trial of a novel therapy to treat stroke after the study medication failed to produce any measurable improvements in outcomes and the two groups receiving different doses of the

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in research that contributes substantively to medical knowledge impotent, useless, or fraudulent.

*Id.* at 2129-30. Of course, IRBs cannot foresee such developments and therefore cannot take them into account in the initial process of weighing risk and benefit.

<sup>266</sup> *A Furor over “Super-Aspirin,”* NEWSDAY, Jan. 30, 2001, at C5.

<sup>267</sup> *Id.* (noting that the death rate for patients on the study drug was 2.7% versus 2.0% for patients receiving placebo, resulting in 30 additional deaths among patients on the study drug arm).

<sup>268</sup> After the data from the fifth study became available, the PI called for an immediate cessation of the research. *Id.* (adding that many of the unexpected deaths apparently were due to cardiac arrests triggered by blood clots, which super-aspirin was intended to prevent). Stay tuned for a large class-action lawsuit.

study medication experienced higher death rates than those receiving placebo.<sup>269</sup> More recently, researchers called a halt to a massive study of hormone replacement therapy in post-menopausal women after the data demonstrated measurable increases in the risk of breast cancer and heart disease.<sup>270</sup>

Courts must recognize that research protocols are designed to discover unknown information about the safety and efficacy of a particular therapy, and that the very nature of research suggests that reviewing boards must assess the risks and scientific value of the research without complete information. Although retrospective analysis of data may demonstrate that an IRB should have halted research earlier, or never approved it in the first place, courts should not permit hindsight to serve as the sole basis for a negligence claim against a reviewing board. Instead, the negligence inquiry should focus on the appropriateness of the IRB's judgments based on what was reasonably knowable at the time of approval.<sup>271</sup> Only if the IRB fails to require or adequately incorporate all available information in its decisionmaking process—or fails to respond to interim data—should the board be held responsible for injuries to participants.

#### IV. CONCLUSION

Previous commentators have proposed a variety of regulatory reforms to improve the safety of clinical research.<sup>272</sup> Some have advocated a radical restructuring of the existing regulatory system governing human subjects research,

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<sup>269</sup> See Gregory W. Albers et al., *Aptiganel Hydrochloride in Acute Ischemic Stroke: A Randomized Controlled Trial*, 286 JAMA 2673 (2001) (noting that the death rate among those receiving the high dose of the study drug was 26.3%, compared with 19.2% among those in the placebo group).

<sup>270</sup> See Gina Kolata, *Study is Halted Over Rise Seen in Cancer Risk*, N.Y. TIMES, July 9, 2002, at A1. The same question also recently arose for men in the context of a massive study of a prostate cancer prevention therapy. See Abigail Zuger, *A Big Study Yields Big Questions*, 349 NEW ENG. J. MED. 213, 213 (2003) (describing the decision to halt a study of a prostate cancer inhibitor when it became apparent that “the drug did indeed significantly reduce the prevalence of prostate cancer but did so at a disturbing price: the possibility that if cancer is detected, it may be of a higher pathological grade”).

<sup>271</sup> Courts generally will not impose a duty to warn of unknowable risks associated with drugs or other medical technologies. Cf. *Klisch v. MeritCare Med. Group, Inc.* 134 F.3d 1356, 1359 (8th Cir. 1998); *Mallett v. Pirkey*, 466 P.2d 466, 470 (Colo. 1970); *Moore v. Vanderloo*, 386 N.W.2d 108, 116 (Iowa 1986); *Tanuz v. Carlberg*, 921 P.2d 309, 315 (N.M. Ct. App. 1996); *Castrignano v. E.R. Squibb & Sons, Inc.*, 546 A.2d 775, 782 (R.I. 1988).

<sup>272</sup> See, e.g., Michael Baram, *Making Clinical Trials Safer for Human Subjects*, 27 AM. J.L. & MED. 253 (2001) (paying particular attention to safety issues in clinical trials of biotechnology and gene therapies); Jesse A. Goldner, *An Overview of Legal Controls on Human Experimentation and the Regulatory Implications of Taking Professor Katz Seriously*, 38 ST. LOUIS U. L.J. 63, 104-12 (1993) (discussing non-tort mechanisms for improving IRB performance and accountability); Jonathan Moreno et al., *Updating Protections for Human Subjects Involved in Research*, 280 JAMA 1951 (1998) (emphasizing the need for better protection of vulnerable populations, and suggesting ways to improve IRB efficiency); Woodward, *supra* note 32, at 1949-52; see also INST. OF MED., RESPONSIBLE RESEARCH: A SYSTEMS APPROACH TO PROTECTING RESEARCH PARTICIPANTS (2003), available at [www.nap.edu/execsumm/0309084881.html](http://www.nap.edu/execsumm/0309084881.html) (last visited July 1, 2004).

recommending, for example, that Congress create an independent Human Subjects Protection Agency with complete rulemaking and adjudicatory authority over all human research.<sup>273</sup> Such a centralized system of research oversight would make it possible to publish IRB decisions in difficult cases in a process analogous to common law, which would in turn establish some consistency in the resolution of close questions that are currently left to the discretion of individual IRBs.<sup>274</sup>

Others urge caution, however, in considering additional layers of regulatory safeguards for clinical research, noting that research is by definition a risky undertaking, and suggesting instead that clinical investigators redouble their efforts to use sound scientific design for their protocols, avoid conflicts of interest, and obtain full informed consent from participants.<sup>275</sup> Short of creating an entirely new agency, OHRP desperately needs additional resources to enforce existing regulatory requirements,<sup>276</sup> and local IRBs require improved institutional support and staffing.<sup>277</sup> Commentators also strongly advocate improved, mandatory education of clinical investigators and IRB members in order to reduce the risk of errors that might harm research subjects.<sup>278</sup> These sorts of reforms undoubtedly will produce incremental improvement in the system of research protections but

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<sup>273</sup> See George J. Annas, *Regs Ignored in Research*, NAT'L L.J., Nov. 15, 1999, at A20; Wendy K. Mariner, *Human Subjects*, NAT'L L.J., May 13, 2002, at A25 (calling for a wholly independent "federal agency to regulate all research with human subjects" whether publicly or privately funded); see also Marc Kaufman, *Clinical Trial Sanctions Urged: HHS Plans to Tighten Controls to Protect Patients in Tests*, WASH. POST, May 24, 2000, at A2 (reporting that the Clinton administration asked Congress to authorize fines of up to \$250,000 against individual scientists who violate research regulations and fines of up to \$1 million against non-compliant institutions, and that HHS wants to improve IRB training and direct monitoring of patients during in-progress clinical trials). Legislation designed to fill gaps in the existing regulatory scheme has been proposed but not yet enacted. See, e.g., Human Research Subject Protections Act of 2000, H.R. 4605, 106th Cong. (2000) (proposing to extend federal regulations to all research involving human subjects, whether or not federally-funded, including research conducted by private companies and individuals).

<sup>274</sup> See Coleman, *supra* note 47; Katz, *supra* note 65, at 39-40 (observing that the lack of a centralized policy-formulating board leaves these "painful decisions" to the "low visibility handiwork of local IRBs"). But see Noah, *supra* note 46 (doubting that such a system would work).

<sup>275</sup> Arthur Caplan & David Magnus, *Overregulating Research*, CHI. TRIB., Dec. 21, 1999, at 31; Mosk, *supra* note 168, at B7 (discussing concerns about the potential chilling effect of liability on medical research, and describing legislation under consideration in Maryland that offers immunity from suits for medical researchers who comply with federal regulations); see also Elliot Foucar, Letter to Editor, *How Much Oversight is Necessary to Protect Human Subjects?*, 287 JAMA 716, 717 (2002) (arguing that over-regulation "imposes a legal 'tax' on research, similar to the highly inefficient tort tax imposed on clinical medicine").

<sup>276</sup> At present, OHRP employs only forty-seven people, including only five investigators. In 2001, OHRP investigated only one percent of unexpected adverse event reports—approximately 100 incidents—and investigated on site in only four of those cases. See Kranish, *supra* note 25, at A1. Overall, however, FDA and OHRP have stepped up enforcement of federal human subjects protections since the issuance of the 1998 reports. See HHS Status Report, *supra* note 8, at 9.

<sup>277</sup> See Hoffman, *supra* note 76, at 748-53.

<sup>278</sup> See, e.g., Gary B. Ellis, *Keeping Research Subjects out of Harm's Way*, 282 JAMA 1963, 1963-64 (1999); Moreno et al., *supra* note 272, at 1955-56.

may do little to change the underlying culture of medical research which, for too long, has placed the demands of science above the needs of the individual patient.

A variety of changes in the human research “machine,” including overwork, lack of expertise and training, and greater conflicts of interest, pose formidable challenges to the protection of human subjects and likely will serve as a basis for a proliferation of negligence claims against IRBs and the institutions that house them. This litigation trend is not necessarily cause for hand-wringing. Although IRBs strive to protect human research subjects from harm and are largely successful in their efforts, these boards labor under less than ideal circumstances that contribute to a tendency towards shortcuts and misjudgments. The regulations serve as a starting point for resolving difficult ethical and scientific problems in proposed research, but truly effective human subjects protection requires IRBs to exceed the minimal regulatory requirements for the protection of research subjects.

This endeavor will require more financial and institutional support, better training, and more specialized expertise. Institutions also must work to foster a cooperative mindset between clinical researchers and the supervising IRB, helping researchers to view the board as a partner in clinical investigations—an entity that can help to assure the highest ethical standards and thereby protect the value and validity of the scientific results—rather than as an obstacle to successful research. Increased regulatory surveillance and guidance also may help to enhance IRB performance. Courts certainly ought to be attentive to concerns about broad expansion of IRB duties of care. Realistically, however, holding IRBs accountable in negligence for the injuries that result from their shortcomings will serve as an efficient catalyst for meaningful improvement to the system of human subjects protections.