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INSTITUTIONAL CONFLICTS AND RESPONSIBILITIES IN AN AGE OF ACADEMIC-INDUSTRY ALLIANCES

MICHAEL J. MALINOWSKI, JD*

INTRODUCTION

This is an extraordinary time for life science and health care. Never has so much research in science been applied commercially, and never have so many human clinical trials been underway and offered so much promise for improving human health.¹ Consequentially, never have the economic and regulatory challenges been as great.²

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1. See *infra* notes 3-7 and accompanying text. See generally NAT'L ACAD. OF SCIENCES, INST. OF MED., EXTENDING MEDICARE REIMBURSEMENT IN CLINICAL TRIALS (Henry J. Aaron & Hellen Gelband eds., 2000) [hereinafter MEDICARE REIMBURSEMENT IN CLINICAL TRIALS], available at <http://www.nap.edu/index.html>; PHRMA, THE PHARMACEUTICAL INDUSTRY PROFILE 2000 v (2000) [hereinafter PHRMA INDUSTRY PROFILE], at http://www.phrma.org/publications/publications/profile00/PhRMA_ExecSum.pdf. According to Ernst & Young, more than 280 biotech products are in advanced clinical trials. ERNST & YOUNG, CONVERGENCE: THE BIOTECHNOLOGY INDUSTRY REPORT 44 (2000). For identification of the drug development pipeline, see <http://www.phrma.org> (last visited Aug. 23, 2001) (site of the Pharmaceutical Researcher and Manufacturers of America (PhRMA), the leading pharmaceutical trade organization); <http://www.bio.org> (last visited Aug. 23, 2001) (site of the Biotechnology Industry Organization (BIO), the leading biotechnology industry trade organization); <http://www.clinicaltrials.gov> (last visited Aug. 23, 2001) (details on approximately 5,500 mostly government-funded clinical trials); <http://cancertrials.nci.nih.gov> (last visited Aug. 23, 2001) (the National Cancer Institute's clinical trial listing); <http://actis.org> (last visited Aug. 23, 2001) (the AIDS clinical trials information service (ACTIS)); <http://www.centerwatch.com> (last visited Aug. 23, 2001) (one of the earliest and the most comprehensive private sites focusing on clinical trials); <http://www.emergingmed.com> (last visited Aug. 23, 2001) (privately-funded cancer trials under expansion to cover other diseases); <http://www.veritasmedicine.com> (last visited Aug. 23, 2001) (lists trials and standard treatments for numerous diseases); <http://www.americasdoctor.com/clintrials/main.cfm> (trials in seven disease categories, excluding cancer); and <http://www.acurian.com/patient> (last visited Aug. 23, 2001) (developing lists of trials in various disease categories).

2. See Michael J. Malinowski, *FDA Regulation of Biotechnology Products for Human Use*, in 1 ENCYCLOPEDIA OF ETHICAL, LEGAL, AND POLICY ISSUES IN BIOTECHNOLOGY 215, 223-25 (Thomas J. Murray & Maxwell J. Mehlman eds. 2000) [hereinafter *FDA Regulation*]; Michael J. Malinowski, *Biotechnology in the USA: Responsive Regulation in the Life Science Industry*, 2 INT'L J. BIOTECHNOLOGY 16, 17 (2000) [hereinafter *Biotechnology in the USA*]. See generally MICHAEL J. MALINOWSKI, BIOTECHNOLOGY: LAW, BUSINESS AND REGULATION § 9.05 (1999 & Supp. 2001). [hereinafter BIOTECHNOLOGY].

Biotechnology has become a driving force in life science and increasingly in health care.³ The now maturing biotechnology sector has infused immense innovation and capital into life science research and development (R&D).⁴ Also, the pharmaceutical industry has been allocating a rising percentage of its revenues to research, from 11 percent to 20.3 percent over the last twenty years.⁵ The

3. Consider that during the time frame for standard drug development (8-12 years) we have witnessed the emergence of biotechnology as a global industry and the market introduction of nearly 100 drugs developed with this technology. See generally CYNTHIA ROBBINS-ROTH, FROM ALCHEMY TO IPO: THE BUSINESS OF BIOTECHNOLOGY ix (2000); *Biotechnology Industry Organization (BIO)* at <http://www.bio.org> (last visited Aug. 23, 2001) (the world's foremost biotech trade organization, identifying market approved drugs developed with the use of biotechnology). Nevertheless, the technology associated with contemporary biotechnology—meaning biotechnology undertaken in the era of the Human Genome Project (HGP)—we have seen applied thus far, and the impact of this technology on academia, industry, the health care establishment, and people's lives merely marks the beginning of a profound transition in both research and health care. See RICHARD W. OLIVER, THE COMING BIOTECH AGE: THE BUSINESS OF BIO-MATERIALS (2000) (discussing the broad human health and economic impact of advances in human genetics and biotechnology). See also Juan Enriquez & Ray A. Goldberg, *Transforming Life, Transforming Business: The Life-Science Revolution*, HARV. BUS. REV. 96, 97 (2000) (predicting a convergence among traditionally distinct sectors into life science). Drug development and medicine are moving into an era of unprecedented precision, most notably through the coupling of biology and information technology (bioinformatics) to identify gene expression, including subtle genetic differences known as single nucleotide polymorphisms (SNIPS) which are associated with the responsiveness of individuals to pharmaceuticals (both positive and adverse reactions). See Michael J. Malinowski, *Separating Predictive Genetic Testing from Snake Oil: Regulation, Liabilities, and Lost Opportunities*, 41 JURIMETRICS 23, 31-33 & app. (2000) [hereinafter *Snake Oil*] (identifying enabling technologies and emerging scientific disciplines). See also Sharon Begley, *Made-to-Order Medicine*, NEWSWEEK, June 25, 2001, at 64; Brad Stone, *Wanted: Hot Industry Seeks Supergeeks*, NEWSWEEK, Apr. 30, 2001, at 54, 55 (discussing initiatives in bioinformatics by major universities and "computer-industry giants" such as Compaq, IBM, and Oracle). "Increasingly, the medical community is debating *when* rather than *whether* one's DNA will enable health care providers to assess susceptibility to common diseases, improve preventive care, and predict reactions to medications and other treatments." *Snake Oil*, *supra*, at 31. In fact, instances of genetic profiling for drug delivery already have reached the market. For example, breast cancer patients are tested for over expression of Her-2-neu to determine whether they are candidates for Herceptin, and Visible Genetics, Inc. is marketing a test that helps doctors choose among the 15 or so drugs available to treat individual patients for AIDS. *Id.* at 26 n.12, 31-32 n.31; Andrew Pollack, *When Gene Sequencing Becomes a Fact of Life*, N.Y. TIMES, Jan. 17, 2001, at C1.

4. Jeffrey Krasner, *Biotech Cashes In*, BOSTON GLOBE, June 27, 2001, at C1. The tools of biotechnology have integrated the biotechnology and pharmaceutical sectors and are causing a convergence of many traditionally distinct industry sectors. See generally ERNST & YOUNG, *supra* note 1; Enriquez & Goldberg, *supra* note 3.

5. PHARMA INDUSTRY PROFILE, *supra* note 1, at 20. See Ronald Rosenberg, *Data Bottleneck Slowing Drug Discovery*, BOSTON GLOBE, June 20, 2001, at D4. According to PHARMA, over the last decade the average cost of discovering and developing a single drug climbed from \$300 million to \$500 million, with some estimates reaching \$800 million. See PHARMA INDUSTRY PROFILE, *supra*

industry's investment in R&D was \$26.4 billion in the year 2000 and is estimated to reach \$30 billion this year, compared to only \$2 billion a decade ago.⁶ Government investment in biomedical research is also at an all-time high and rising.⁷

For better and for worse, biotechnology has fundamentally changed the culture of research through the integration of academia and industry, and by placing intense focus on commercial application.⁸ The environment for drug

note 1, at vi; PHRMA, A MONTHLY REPORT FROM AMERICA'S PHARMACEUTICAL COMPANIES (Mar. 2001), at <http://www.phrma.org> (last visited Aug. 23, 2001). This increased investment in R&D reflects the fact that the pharmaceutical industry, after decades of solid profitability, now must overcome some Herculean challenges to meet shareholder expectations. See *FDA Regulation*, *supra* note 2, at 224-225, (addressing the challenges faced by pharmaceutical developers in the new millennium). For example, many of the industry's most profitable pharmaceuticals have gone off patent and many more patents will expire over the next few years. Also, drug pricing is being challenged domestically and globally (e.g., the dispute over African nations' access to AIDS pharmaceuticals), and patient markets are fracturing through advances in human genetics which are raising precision in drug development significantly and splintering traditional disease classifications through genetic profiling. *Id.* See generally CTR. FOR INT'L DEV. AT HARVARD UNIV., GLOBAL GOVERNANCE OF TECHNOLOGY: MEETING THE NEEDS OF DEVELOPING COUNTRIES, SYNTHESIS REPORT (June 2001), at http://www.cid.harvard.edu/cidbiotech/globalgovconf/report_abstract.htm (last visited Aug. 23, 2001); Jeffrey D. Sachs, *Balms for the Poor*, THE ECONOMIST, Aug. 14, 1999; BOSTON CONSULTING GROUP, THE PHARMACEUTICAL INDUSTRY INTO ITS SECOND CENTURY: FROM SERENDIPITY TO STRATEGY (Jan. 1999). Today, there are approximately 3,000 drugs on the market that act against diseases associated with approximately 483 drug targets. Rosenberg, *supra*, PHRMA INDUSTRY PROFILE, *supra* note 1. In contrast, through fields such as genomics, proteomics, and bioinformatics, the pharmaceutical industry anticipates identifying 3,000 to 10,000 targets over the next several years. See PHRMA INDUSTRY PROFILE, *supra* note 1, at v. See also Rosenberg, *supra*, *Snake Oil*, *supra* note 3, at 32-33 & app. (discussing the impact of genetic profiling on drug development and identifying related science disciplines and technologies). See generally ROBBINS-ROTH, *supra* note 3 (addressing how utilization of combinatorial chemistry, microarrays, laboratory automation and bioinformatics are increasing processing and identification of drug targets exponentially). Automated "high-throughput" equipment is enabling researchers to test thousands of potential drug candidates simultaneously. See PHRMA INDUSTRY PROFILE, *supra* note 1; *Snake Oil*, *supra* note 3, at 32-33 & app. (discussing the impact of genetic profiling on drug development and identifying related science disciplines and technologies).

6. PHRMA INDUSTRY PROFILE, *supra* note 1, at 20-21.

7. See INST. OF MED., FUNDING HEALTH SCIENCES RESEARCH 32 (1990). The Nat'l. Institutes of Health budget, which reached \$17.8 billion in 1999, has more than doubled over the last 10 years. See National Institutes of Health, at <http://www.nih.gov/about/almanacs/index.html> (last visited Aug. 23, 2001). Moreover, in fiscal Year 1999, Congress and the Clinton Administration "produced a commitment to double the funding for NIH by 2003." NAT'L INST. OF HEALTH, INVESTMENTS, PROGRESS, & PLANS: SELECTED EXAMPLES FROM FY 1999-2003, at <http://www.nih.gov/about/investments.htm> (last visited Aug. 23, 2001).

8. See generally U.S. GEN. ACCOUNTING OFFICE, TECHNOLOGY TRANSFER: ADMIN. OF THE BAYH-DOLE ACT BY RESEARCH UNIVERSITIES, GAO/RCED-98-126 (May 1998) [hereinafter GAO REPORT], available at <http://www.access.gpo.gov>; Peter S. Arno & Michael H. Davis, *Why*

development has become a complicated, dynamic entanglement of alliances, corporate partnerships, and licensing and service agreements among biotech companies, pharmaceutical companies, academic institutions, and contract service providers.⁹ With the maturation of science associated with hundreds of biotechnology companies established in the United States in the late 1980s and early 1990s, this environment of intense collaboration, competition, and commercialization is moving into the clinic.¹⁰

This article focuses on the impact of biotechnology and the genetics revolution on clinical research, and the resulting issue of institutional conflicts of interest. A major premise is that the issue of conflicts of interest transcends and requires reforms to the regulatory regimes for both technology transfer and human subject protections. Part I addresses the integration of academia and industry in biomedical research, which has given rise to a proliferation of conflicts of interest. Part II explores how this integration and the wave of resulting innovation in life science R&D is carrying forward from basic research into clinical research, and how the distinction between clinical research and clinical care is being muddled. Part III identifies the regulatory challenges faced by research institutions and the entities regulating them in this era of academia-industry integration. The discussion attributes the issue of potentially pervasive conflicts of interest to weaknesses in the underlying regulatory regimes for federal technology transfer and human subject protections. Part IV introduces proposals for reform.

Don't We Enforce Existing Drug Price Controls? The Unrecognized and Unenforced Reasonable Pricing Requirements Imposed Upon Patents Deriving in Whole or in Part from Federally Funded Research, 75 TUL. L. REV. 631 (2001); David Blumenthal et al., *Participation of Life-Science Faculty in Research Relationships with Industry*, 335 NEW ENG. J. MED. 1734 (1996); John M. Golden, *Biotechnology, Technology Policy, and Patentability: Natural Products and Invention in the American System*, 50 EMORY L.J. 101, 120 (2001); Arti Kaur Rai, *Regulating Scientific Research: Intellectual Property Rights and the Norms of Science*, 94 NW. U.L. REV. 77 (1999) [hereinafter *Regulating Scientific Research*]; Peter D. Blumberg, Comment, *From "Publish or Perish" to "Profit or Perish": Revenues From University Technology Transfer and the §501(c)(3) Tax Exemption*, 145 U. PA. L. REV. 89 (1996); Lisa Piercey, *Technology Transfer Goes Professional*, BIOVENTURE VIEW, Dec. 1998, at 9; Eyal Press & Jennifer Washburn, *The Kept University*, ATLANTIC MONTHLY, Mar. 2000, at 39. According to a recent study, 28% of life sciences faculty received private sponsor funding, 15% held equity in the private sponsor, 33% were engaged in paid consulting arrangements, and 32% held board positions. See Elizabeth A. Boyd & Lisa A. Bero, *Assessing Faculty Financial Relationships With Industry: A Case Study*, 284 JAMA 2209, 2209-10 (2000).

9. See ERNST & YOUNG, *supra* note 1, at 48-49. See generally *supra* note 8 and accompanying text; Michael J. Malinowski & Maureen A. O'Rourke, *A False Start? The Impact of Federal Policy on the Genotechnology Industry*, 13 YALE J. ON REG. 163, 180-88 (1996).

10. See sources cited *supra* note 1. See also PHARMA, 2000 SURVEY: NEW MEDICINES IN DEVELOPMENT: BIOTECHNOLOGY, at <http://www.phrma.org/searchcures/newmeds/> (last visited Aug. 23, 2001).

I. AN ERA OF ACADEMIC-INDUSTRY ALLIANCES

The United States' accomplishments in advancing biotechnology and its commercialization rest upon an aggressive federal technology transfer policy implemented through legislation enacted in the 1980s and early 1990s.¹¹ The policy has been enormously effective in its goal of applying federally-funded research.¹² The methodology is to grant clear title to inventions arising from government-sponsored research to institutions, and to reduce funding agency rights to a nontransferable, nonexclusive government license for non-commercial use.¹³ Reflective of the intent behind the legislation and the stipulation that institutions exercising their options under Bayh-Dole pursue commercial development, many leading research universities approach technology transfer as the means to develop and apply research that otherwise might be delegated to filing cabinets.¹⁴ Technology transfer also generates significant revenue streams

11. This legislation consists of The Bayh-Dole Act, 35 U.S.C. §§ 200-212 (1994). The legislation to implement the Bayh-Dole Act consists of the Stevenson-Wydler Technology Innovation Act of 1980, 15 U.S.C. §§ 3701-3717 (1994); Exec. Order No. 12591 52 Fed. Reg. 13,414 (Apr. 22, 1987); American Technology Preeminence Act of 1991, Pub. L. No. 102-245, 106 Stat. 7 (codified in scattered sections of 15 U.S.C. and 42 U.S.C.); National Technology Transfer and Advancement Act of 1995, Pub. L. No. 104-113, 110 Stat. 775 (codified in scattered sections of 15 U.S.C.). This federal technology transfer policy was complemented by several other areas of policy enacted lockstep with the development and needs of the biotechnology industry, including the Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,302 (June 26, 1986) (issued by the Office of Science and Technology Policy under the Reagan Administration); Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (codified as amended at 21 U.S.C. §§ 360aa-360ee; 26 U.S.C. § 45C (1994); 42 U.S.C. § 236 (1994)); Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (codified in scattered sections of 21 U.S.C.); and the Reauthorization of the Prescription Drug User Fee Act of 1992 ("PDUFA II"), Pub. L. No. 102-571, 106 Stat. 4491 (codified in scattered sections of 21 U.S.C.). The orchestration of these policies and their effectiveness is addressed in *Biotechnology in the USA*, *supra* note 2, at 17-18. For a technical law treatment, see BIOTECHNOLOGY, *supra* note 2, at ch. 8.

12. See generally GAO REPORT, *supra* note 8, at 2. The number of academic patents has risen from approximately 250 annually in the early 1970's to more than 3,100 in 1998. See NAT'L SCI. BD., SCIENCE & ENGINEERING INDICATORS 2000, 6-4 (2001), at <http://www.nsf.gov/sbe/srs/seind00/inro.htm>. According to the Association of University Technology Managers (AUTM), a nonprofit organization of professionals involved in the management of intellectual property and licensing, 1998 filings exceeded 4800. See Mildred K. Cho et al., *Policies on Faculty Conflicts of Interest at US Universities*, 284 JAMA 2203, 2203 (2000). See also ASS'N UNIV. TECH. MANAGERS, INC., AUTM LICENSING SURVEY: FY 1999 10-12 (2000) [hereinafter AUTM SURVEY], available at <http://www.autm.net/surveys/99/survey99A.pdf> (last visited Aug. 14, 2001).

13. GAO REPORT, *supra* note 8, at 2 (referring to a section of a letter from Senator Orrin G. Hatch and Representative Henry Hyde).

14. *Id.* For example, the Massachusetts Institute of Technology (M.I.T.) has incorporated this position into its mission statement. See MASSACHUSETTS INST. OF TECH., TECHNOLOGY LICENSING OFFICE MISSION STATEMENT, available at <http://web.mit.edu/afs/athena.mit.edu/>

to cover administrative costs and to advance subsequent research.¹⁵ Moreover, resulting collaborations can be the means for researchers to access proprietary research tools and enabling technologies essential for contemporary biomedical research, including voluminous deoxyribonucleic acid (DNA) libraries, databases, and the bioinformatics capabilities to use these technologies.¹⁶

The federal technology transfer legislation enacted by Congress mandates an impact assessment every five years, the last of which was completed via a *Report to Congressional Committees* issued by the General Accounting Office (GAO) in May 1998.¹⁷ The GAO report documents that Bayh-Dole is accomplishing its primary objective: much more academic research is being applied, especially when measured by the increase in patent filings and the establishment and expansion of university technology transfer operations.¹⁸ This conclusion is substantiated further by more recent data provided by the United States Patent and Trademark Office (USPTO)¹⁹ and observations about the intensity of ongoing university technology transfer undertakings by the nation's leading research universities.²⁰ In fact, through a study released in August 2001, the National Institutes of Health (NIH) responded to proposals that more conditions be placed on its biomedical research funding.²¹ The NIH warned that recouping commercial

org/t/to/www/mission.html.

15. Some renowned institutions, including M.I.T., also generate significant revenues by offering personalized technology transfer services to pharmaceutical and biotechnology companies for an annual fee that may reach tens of thousands of dollars per company. See MASSACHUSETTS INST. OF TECH., TECHNOLOGY LICENSING OFFICE: FURTHER INFORMATION, at <http://web.mit.edu/afs/athena.mit.edu/org/t/to/www/moreinfo.html> (last visited Sept. 12, 2001).

16. One of the most noteworthy collaborations is the functional genomics initiative undertaken by the Whitehead Institute for Biomedical Research, Millennium Pharmaceuticals, Inc., Affymetrics, Inc. and Bristol Myers Squibb. See Press Release, Whitehead Institute for Biomedical Research, "SOMs" Help Analyze Thousands of Genes (Mar. 12, 1999), at http://www.whitehead.mit.edu/nap/1999/nap_press_99.html (last visited Aug. 23, 2001).

17. See generally, GAO REPORT, *supra* note 8.

18. See *supra* note 12. See generally GAO REPORT, *supra* note 8, at 2 (relying heavily upon data compiled by AUTM).

19. The United States Patent and Trademark Office (USPTO) reports that biotechnology is one of the areas leading the 12.3% growth of utility, plant, and reissue (UPR) patent applications in fiscal year 2000. United States Patent & Trademark Office, *Annual Reports: 2000 Annual Report*, available at <http://www.uspto.gov/web/offices/com/annual/index.html> (last visited Nov. 1, 2001). The USPTO has added over 800 examiners since 1999 and anticipates another 12% increase in UPR filings for fiscal year 2001. *Id.*; United States Patent & Trademark Office, *Annual Reports: 1999 Annual Report*, available at <http://www.uspto.gov/web/offices/com/annual/index.html> (last visited Nov. 1, 2001).

20. See Press & Washburn, *supra* note 8, at 46; Piercey, *supra* note 8. See generally *supra* note 8; AUTM SURVEY, *supra* note 12.

21. See generally DEPT HEALTH & HUMAN SERVS., NAT'L INST. OF HEALTH, NIH RESPONSE TO THE CONFERENCE REPORT REQUEST FOR A PLAN TO ENSURE TAXPAYERS' INTERESTS ARE PROTECTED (July 2001) [hereinafter NIH RESPONSE], available at <http://www.nih.gov/news/>

profits through royalty payments might discourage extensive research funded jointly by government and industry.²²

II. THE METAMORPHOSIS OF CLINICAL RESEARCH

The cultural changes in academia and concerns about conflicts of interest associated with academic-industry integration in basic research²³ now have reached the clinic. With the maturation of the Human Genome Project (HGP) and associated biomedical science, the integration of academia and industry has carried forward into clinical research at the same time that clinical research is being integrated with patient care.²⁴ Given a generation of breakthrough pharmaceuticals in R&D, the standard of care for many conditions is arguably in Phase III and even Phase II clinical trials.²⁵ Increasingly, this is the public's perception. Influenced by the promise of genetic medicine and accomplishments such as the introduction of drugs such as Avonex for multiple sclerosis²⁶ and

070101wyden.htm. See also Anthony Shadid, *A US Share of Royalties on Research is Opposed: NIH Report Warns of Focus on Profit*, BOSTON GLOBE, Aug. 22, 2001, at A1. As concluded by NIH, "[r]equiring direct financial recoupment of the federal investment in biomedical research can potentially impede the development of promising technologies by causing industry to be unwilling to license federally funded technologies. The 'reasonable pricing' provisions that NIH once required in all CRADA [Cooperative Research and Development Agreement] and exclusive license negotiations did just that." NIH RESPONSE, *supra*, at pt. F. For a contrary opinion, see Arno & Davis, *supra* note 8 (calling for the imposition of price controls). Similarly, Arti Rai has proposed that anticipated cost reductions in research and development attributable to utilization of genomics to streamline and accelerate trials be used as a basis for "scaling back" patent protection for pharmaceuticals. See Arti K. Rai, *The Information Revolution Reaches Pharmaceuticals: Balancing Innovation Incentives, Cost, and Access in the Post-Genomics Era*, 2001 U. ILL. L. REV. 173, 173 (2001). However, presumably use of pharmacogenomics, bioinformatics, and related technologies will result in pharmaceuticals tailored to individual genetic profiles, streamlined therapeutic use, regulatory approval and labeling limitations, and will significantly fraction traditional disease classifications and pharmaceutical markets. See FDA Regulation, *supra* note 2, at 224. See also Snake Oil, *supra* note 3, at 31-33. Although industry may offset some of this market reduction through the introduction of preventive uses for pharmaceuticals, the days of relatively crude pharmaceuticals enjoying broad off-label use for the full term of their patents are the past, not the future, of life science. See *id.* See also *supra* note 5.

22. See Shadid, *supra* note 21. See generally NIH Response, *supra* note 21.

23. See generally Rai, *supra* note 8.

24. Cf. MEDICARE REIMBURSEMENT IN CLINICAL TRIALS, *supra* note 1.

25. See *supra* notes 1, 10 and accompanying text. But see Patricia C. Kuszler, *Curing Conflicts of Interest in Clinical Research: Impossible Dreams and Harsh Realities*, 8 WIDENER L. SYMP. J. 115, 137 (2001) (citing David Korn, *Conflicts of Interest in Biomedical Research*, 284 JAMA 2234 (2001)). "Researchers tend to be passionate and committed to their research hypothesis and may believe that it does offer the best hope for alleviation of pain and suffering, even though the preliminary research results are not confirmatory." *Id.*

26. Avonex is manufactured by Biogen, Inc. of Cambridge, Massachusetts.

Herceptin²⁷ for advanced cases of breast cancer, many in the public now perceive clinical research as embodying the most innovative and promising treatment options. The public is seeking access,²⁸ and the advent of information technology is helping to make access possible. Internet sites, including NIH's and the National Library of Medicines' listing of clinical trials,²⁹ are linking patients and trials.

In light of the towering and still rising wave of information, the all-knowing general practitioner is not a contemporary possibility. Overwhelmed with present challenges in an age of managed care, some providers understandably welcome patient self-assertiveness. Similarly, teaching hospitals are no longer able to subsidize research through billing, and many have been pushed out of clinical research through the exponential growth of the Contract Research Organization (CRO) industry.³⁰ Several teaching hospitals and acclaimed academic medical research centers are beginning to offer clinical research services to industry in a manner intended to allow them to compete commercially with CROs.³¹

27. Herceptin is manufactured by Genentech, Inc. of South San Francisco, California.

28. From 1995 to 1999, volunteer participation in research increased 39% (from 502,000 to more than 700,000). See Tom Abate, *Maybe Conflicts of Interest are Scaring Clinical Trial Patients: Report that Blames Negative Media Also Cites Complaint Surge*, S.F. CHRON., Apr. 30, 2001, at D1.

29. See <http://www.clinicaltrials.gov>, *supra* note 1 (details on approximately 5,500 mostly government-funded clinical trials). Other government-sponsored sites include the National Cancer Institute's clinical trial listing, at <http://cancertrials.nci.nih.gov/> (last visited Aug. 23, 2001), and the AIDS clinical trial information service (ACTIS), at <http://www.actis.org> (last visited Aug. 23, 2001). There are also several private sites, including the long-established site maintained by CenterWatch, at <http://www.centerwatch.com/> (last visited Aug. 23, 2001); EmergingMed.com, at <http://www.emergingmed.com> (last visited Aug. 23, 2001) (privately-funded cancer trials; expanding to cover other diseases); Veritasmedicine, at <http://www.veritasmedicine.com> (last visited Aug. 23, 2001) (lists trials and standard treatments for 28 diseases); Americasdoctor, at <http://www.americasdoctor.com> (last visited Aug. 23, 2001) (trials in eight disease categories, excluding cancer); and Acurian, at <http://www.acurian.com> (last visited Aug. 23, 2001) (developing lists of trials in 20 disease categories).

30. Leaders in the CRO industry include Covance Inc., at <http://www.covance.com> (last visited Aug. 23, 2001); Parexel International Corporation, at <http://www.parexel.com> (last visited Aug. 23, 2001); and Quintiles Transnational, at <http://www.quintiles.com> (last visited Aug. 23, 2001). This dramatic increase in clinical research has introduced a demand for professionals such as clinical research associates (CRAs) and regulatory compliance officers that exceeds availability. See Ronald Rosenberg, *Growth in New Drugs Creates Need for CRAs: Job Demands Include Monitoring of New Trials*, BOSTON GLOBE, May 6, 2001, at J1.

31. See, e.g., Liz Kowalczyk, *Medical Schools Join Forces: Harvard, Others Aim to Give Drug Firms Faster OK's on Clinical Trials*, BOSTON GLOBE, July 28, 2000, at C1. "Harvard University Medical School and four other top US medical schools, worried that private industry is taking over too much of human research on new medical treatments, have formed an alliance promising drug companies faster approval and completion of critical clinical trials." *Id.*; John Reichard, *Academic Medical Centers Form Research Alliance*, 54 MED. & HEALTH 3 (2000) (clinical trial collaboration among Baylor College of Medicine, the Harvard-affiliated Partners Health System, University of Pennsylvania,

Government policy is responsive to, and even encourages, this convergence of clinical research and clinical care. First, the Food and Drug Modernization Act of 1997 (FDMA) has expanded compassionate use, accelerated review, and approval of innovative, breakthrough drugs via the "fast track."³² The latter has balanced accelerated review and access with more extensive compilation of Phase IV data and oversight.³³ Second, the Food and Drug Administration (FDA) has introduced a comprehensive web site to maximize public access to information about clinical trials.³⁴

Third and most significant, on September 19, 2000, the Health Care Financing Administration (HCFA) announced a final, national coverage decision to immediately cover the routine costs of qualifying clinical trials.³⁵ In addition, Medicare decided to cover reasonable and necessary items and services used in order to diagnose and treat complications arising from participation in all clinical trials.³⁶ This decision is the culmination of HCFA's tendency over the last several years to cover costs associated with clinical research.³⁷ Similarly, at least in recent years, the trend among private payers has been to more readily cover experimental therapies rather than risk litigation and media criticism,³⁸ further

Vanderbilt University, and Washington University School of Medicine).

32. 21 U.S.C. § 356 (Supp. V 1995-2000).

33. *See id.*

34. *See* <http://www.clinicaltrials.gov>, *supra* note 1.

35. *See* HEALTH CARE FINANCING ADMIN., MEDICARE COVERAGE POLICY-CLINICAL TRIALS, FINAL NATIONAL COVERAGE DECISION [hereinafter HCFA DECISION], at <http://www.hcfa.gov/covrage/8d2.htm> (last visited Sept. 4, 2001). *See also* DEP'T OF HEALTH & HUMAN SERVS., HEALTH CARE FINANCING ADMIN., HCFA FACT SHEET, MEDICARE COVERAGE ROUTINE COSTS OF BENEFICIARIES IN CLINICAL TRIALS (2000), at <http://www.hcfa.gov/medlearn/ctfs13.pdf>.

36. *See id.* Coverage under this decision excludes "the investigational item or service, itself, items and services provided solely to satisfy data collection and analysis needs and that are not used in the direct clinical management of the patient . . . ; and items and services customarily provided by the research sponsors free of charge for any enrollee in the trial." HCFA, DECISION, *supra* note 35.

37. *See* MEDICARE REIMBURSEMENT IN CLINICAL TRIALS, *supra* note 1, at 33-34. For example, HCFA has been covering costs associated with 96% of the investigational medical devices in clinical research since 1995. *Id.* at 34.

38. *See generally* GEN. ACCOUNTING OFFICE, HEALTH INSURANCE: COVERAGE OF AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR BREAST CANCER, GAO/HEHS-96-83 (Apr. 24, 1996). "Too often, judicial determinations lack medical and scientific soundness, and innovative medical technologies are forced into use through litigation and legal liability only to be seriously questioned later." *Snake Oil*, *supra* note 3, at 38-39 & n.67 (addressing reliance on a subsequently discredited study for covering thousands of autologous bone marrow transplantations in breast cancer patients). "Courts err and order payment for not only unproven, but dangerous therapies." Kuszler, *supra* note 25, at n.35 (citing Mark R. Tonelli et al., *Clinical Experimentation: Lessons from Lung Volume Reduction Surgery*, 110 CHEST 230, 235 (1996)).

fueling federal and state legislative initiatives to expand patient rights.³⁹ As acknowledged by the Institute of Medicine in its 1996 report on Medicare reimbursement in clinical trials, the American Association of Health Plans generally encourages reimbursement for the routine costs of care associated with NIH-sponsored trials, and several large private health plans have been routinely covering cancer research trials conducted by the National Cancer Institute.⁴⁰

III. REGULATORY CHALLENGES

The threat of pervasive, unchecked conflicts of interest in clinical research, which jeopardize research integrity, the well being of subjects, and public trust, is largely attributable to parallel weaknesses in two of the regulatory regimes fundamental to biomedical research: (1) federal technology transfer; and (2) the protection of human subjects. As discussed below, the weaknesses of each regime are twofold: (1) insufficiencies in the regimes themselves; and (2) a failure of federal agencies to exercise existing discretion and to enforce relevant standards and regulations. Regulations tailored to conflicts of interest simply shadow these insufficiencies by relying heavily upon self-enforcement by funding recipients.

A. Weaknesses in the Regulatory Regime for Technology Transfer

Despite the measurable successes of the United States' federal technology transfer policy,⁴¹ there is also ample reason for concern. As successful as the federal technology transfer regime (illustrated in figure 1) has been in advancing life science, the scheme embodies ridiculously little reliable accountability. Presently, the entire system of federal technology transfer (i.e., distribution of billions of dollars in research funding) is a chain of delegation of accountability which passes through recipient institutions and rests largely with the individual researchers who are being funded.⁴²

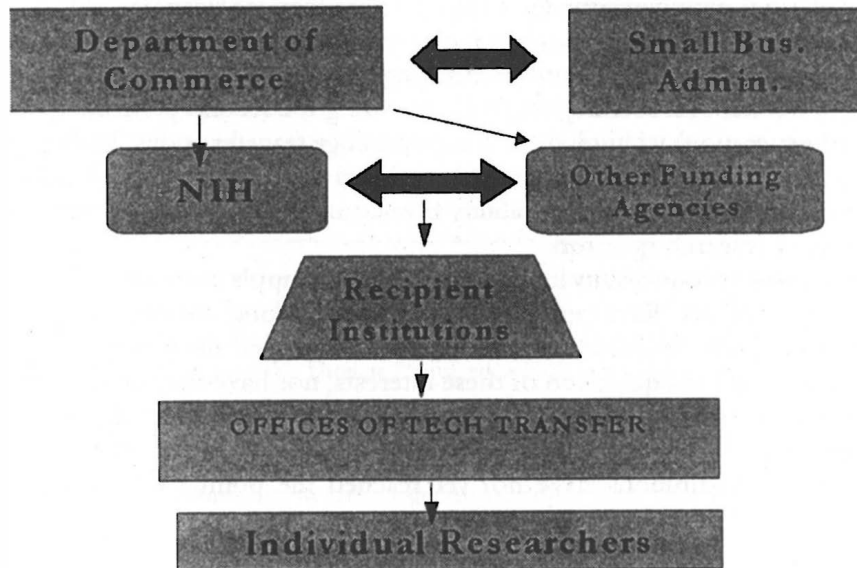
39. See generally David Espo, *Bush Seeks Deal on Patients' Bill*, BOSTON GLOBE, Aug. 1, 2001, at A3; Sue Kirchhoff, *Battle Brews Over Suits vs. HMOs Issue Seen Key To OK of Bill on Patients' Rights*, BOSTON GLOBE, June 18, 2001, at A1.

40. See MEDICARE REIMBURSEMENT IN CLINICAL TRIALS, *supra* note 1, at 30-31, 33-34, 38-40, 45-46.

41. See generally NIH RESPONSE, *supra* note 21; GAO REPORT, *supra* note 8.

42. An analogy can be drawn to having an Internal Revenue Code without the enforcement mechanism of the Internal Revenue Service.

TECHNOLOGY TRANSFER: Implementation / Enforcement



(Figure 1)

Although the federal technology transfer regulations call for the reporting of all inventions developed with federal funding, NIH is the only granting agency with a viable information system, the Edison system, which has taken too long to develop and still awaits uniform implementation.⁴³ In fact, in its report warning against government attempts to recoup investment in biomedical research, NIH readily acknowledges that “[i]t is clear that information relating to inventive discoveries and their commercial development is reported neither systematically nor consistently,”⁴⁴ and that NIH is unable to trace federal funding among commercial pharmaceuticals with reliability.⁴⁵

As stated in the GAO report, funding agencies include requirements in their agreements, but generally rely heavily on research institutions. However, research institutions in turn rely upon their individual researchers who are the ultimate funding recipients.⁴⁶ Although most major universities have introduced extensive, automated information processing systems, the universities often separate administration of grant management from technology transfer

43. GAO REPORT, *supra* note 8, at 3-4.

44. NIH RESPONSE, *supra* note 21, at pt. E.

45. *Id.* at pt. D. NIH calls for the creation of a database that will help NIH determine the role that federal money plays in drug development with precision. *See id.*

46. GAO REPORT, *supra* note 8, at 3.2-3.4.

operations. Further, universities depend heavily upon their individual researchers for day-to-day oversight and compliance with the thousands of material transfers and other technology agreements in operation.⁴⁷ Offices of technology transfer are churning out extraordinary amounts of technology via licensing and other agreements that often encompass voluminous amounts of time and call for constant oversight, reporting, and monitoring. Many of these agreements are ongoing in nature, because they require monitoring for second-generation (and even third-generation) technologies. Yet technology transfer audits, both at the institutional and federal agency level, are few and far between.⁴⁸ In an era of research collaboration, the accountability at issue involves corporate partners as well as agency research sponsors.

Despite these accountability limitations, in order to apply as much research as possible, institutions have quickly moved into taking equity interests.⁴⁹ Unfortunately many institutions have not first developed decisive policies to address issues such as liquidation of these interests, nor have they delegated the management of such interests to outside third parties.⁵⁰ The latter can be price prohibitive, especially given present limitations on technology transfer revenue streams. Most institutions have not yet reached the point of meaningfully exceeding costs.⁵¹

B. Weaknesses in the Regulatory Regime for Protection of Human Subjects

The regulatory regimes to protect human subjects⁵² and scientific integrity largely predate the vast integration of academia and industry promoted through

47. This observation is based upon the author's experience practicing in the field of technology transfer and participation in forums with others engaged in the practice and management of technology transfer.

48. See generally NIH RESPONSE, *supra* note 21.

49. See Piercey, *supra* note 8.

50. This observation is based upon the author's experience practicing in the field, researching university policies, and reported incidents of researchers holding equity interests in their research sponsors. See also Sheryl Gay Stolberg, *Biomedicine Is Receiving New Scrutiny as Scientists Become Entrepreneurs*, N.Y. TIMES, Feb. 20, 2000, at 26 (reporting on incidents involving Dr. Ronald G. Crystal at Cornell University's Weil Medical College, Jeffrey M. Isner at St. Elizabeth's Medical Center in Boston, and Dr. James Wilson at the University of Pennsylvania). See also Cho, *supra* note 12.

51. See MASSACHUSETTS INST. OF TECH., TECH. & LICENSING OFFICE, GUIDE TO THE OWNERSHIP, DISTRIBUTION AND COMMERCIAL DEVELOPMENT OF M.I.T. TECHNOLOGY, at <http://web.mit.edu/tlo/www/guide.1.html> (last visited Aug. 23, 2001).

52. "Human subject" is defined differently under DHHS policy (Common Rule), 45 C.F.R. § 46.102(f) (2000), and FDA policy regulations, 21 C.F.R. § 56.102(e) (2001). Specifically, FDA regulations exclude research limited to data analysis from its definition of human subjects research, while DHHS's definition encompasses analysis of data containing individually identifiable private information. See *id.*

federal technology transfer policy.⁵³ Some of the inadequacies in the regime have captured public and government attention through highly-reported conflicts controversies.⁵⁴ Notable examples include the circumstances surrounding the death of Jesse Gelsinger, an 18-year-old gene-therapy subject in a protocol approved by the University of Pennsylvania;⁵⁵ arguments between academics and companies over the release of clinical data, such as the debate between Immune Response and researchers at the University of California and Harvard University;⁵⁶ journal violations of their own conflicts policies, including the renowned *New England Journal of Medicine*;⁵⁷ and an uncomfortable level of

53. The United States regulatory regime for protection of human subjects and the underlying international accords are discussed in BIOTECHNOLOGY, *supra* note 2, at ch. 9 and in PRICEWATERHOUSE COOPERS, LLP, INSTITUTIONAL REVIEW BOARD (IRB) REFERENCE BOOK (Michele K. Russell-Einhorn & Thomas Puglisi, eds., 2001) [hereinafter IRB REFERENCE BOOK].

54. As stated by Dr. Korn, “[r]ecent reports claiming inadequacies in university systems of protection of human research participants and alleging linkage of individual and institutional financial conflicts of interest to the deaths of research participants sound a clarion call to the academic medical community to come together to address these critical issues.” David Korn, *Conflicts of Interest in Biomedical Research*, 284 JAMA 2234, 2236 (2000).

55. See UNIV. OF PENNSYLVANIA HEALTH SYS., INST. FOR HUMAN GENE THERAPY, PRELIMINARY FINDINGS REPORTED ON THE DEATH OF JESSE GELSINGER, at <http://www.med.upenn.edu/ihgt/findings.html> (last visited Aug. 23, 2001); *Gelsinger v. Trustees of the Univ. of Pa.*, Case No. 000901885 (Ct. Com. Pl., Phila. County, filed Sept. 18, 2000), at <http://www.sskrplaw.com/links/healthcare2.html> (last visited Aug. 23, 2001); Thomas Petzinger Jr., *Yes, Technology Seems to Change Almost Daily. But Some Trends are Likely to Remain in Force for a Long Time*, WALL ST. J., Jan. 1, 2000, at R12.

56. See Eric Niiler, *Company, Academics Argue Over Data*, 18 NATURE BIOTECHNOLOGY 1235 (2000).

57. See Linda A. Johnson, *New England Journal of Medicine Admits Lapses in Ethics Policy*, CHICAGO SUN-TIMES, Feb. 24, 2000, at 21 (reporting that the New England Journal of Medicine admitted violating its financial conflict-of-interest policy 19 times over the past three years in its selection of doctors to review new drug treatments). The primary guidance for conflict of interest management by medical journals is the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, a consensus document issued and subsequently revised by the International Committee of Medical Journal Editors (ICMJE) and allegedly utilized by more than 500 journals. See International Committee of Medical Journal Editors, *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, 277 JAMA 927, 927 (1997). See also *infra* note 58 (beginning in June 2001, ICMJE will require journals to ensure that authors of submitted articles must have final say over their conclusions). For a list of journals that utilize these requirements, see <http://www.icmje.org/jmlst.html> (last visited Sept. 4, 2001). See also Erica Rose, *Financial Conflicts of Interest: How are we managing?*, 8 WIDENER L. SYMP. J. 1, 25-28 (2001). Despite widespread utilization of the ICMJE requirements, according to a report published in the April 2001 issue of *Science and Engineering Ethics* by Sheldon Krinsky and co-authors from the University of California at Los Angeles, “[i]n reviewing 61,134 scholarly articles published in 181 academic journals in 1997, researchers . . . found that just one-half of 1 percent detailed personal financial interests, including consulting arrangements, honorariums, expert witness fees, company equity and stock, and patents.”

correlation between industry sponsorship of clinical research and reporting of favorable results.⁵⁸

Direct federal jurisdiction over human subject research encompasses all research conducted or supported by the federal government and research regulated under a specific federal statute.⁵⁹ At this time, human subject research neither regulated by the FDA (meaning not involving an investigational drug) nor supported by the federal government is not subject to direct federal oversight.⁶⁰ Nevertheless, as a practical matter, in most instances, research will be subject to oversight by multiple federal agencies (such as the Office for Human Research Protection (OHRP), the Department of Health and Human Services (DHHS) and the FDA, which have nearly identical but independent regulations for human subject protection).⁶¹

These regulations are implemented through requirements that accompany federal funding (front-end assurances), and requirements enforced through the FDA as a precondition for accepting data in conjunction with a New Drug Application (NDA) or New Biologic Application (NBA) (post-hoc audits).⁶² The former, the fundamental regulations implementing federal policy known as the

Sheryl Gay Stolberg, *Scientists Often Mum About Ties To Industry*, N. Y. TIMES, Apr. 25, 2001, at A17. Moreover, those disclosures all appeared in just one-third of the 181 journals. *Id.*

58. According to a study reviewing clinical trials for cancer drugs, trials "funded by pharmaceutical companies were nearly 8 times less likely to reach unfavorable qualitative conclusions than nonprofit-funded studies." Mark Friedberg et al., *Evaluation of Conflict of Interest in Economic Analyses of New Drugs Used in Oncology*, 282 JAMA 1453, 1455 (1999). In May 2001, ICMJE agreed to establish a new policy to ensure that "authors of articles submitted to their publications must have final say over the conclusions." See *Research Without Spin*, BOSTON GLOBE, Aug. 9, 2001, at A18.

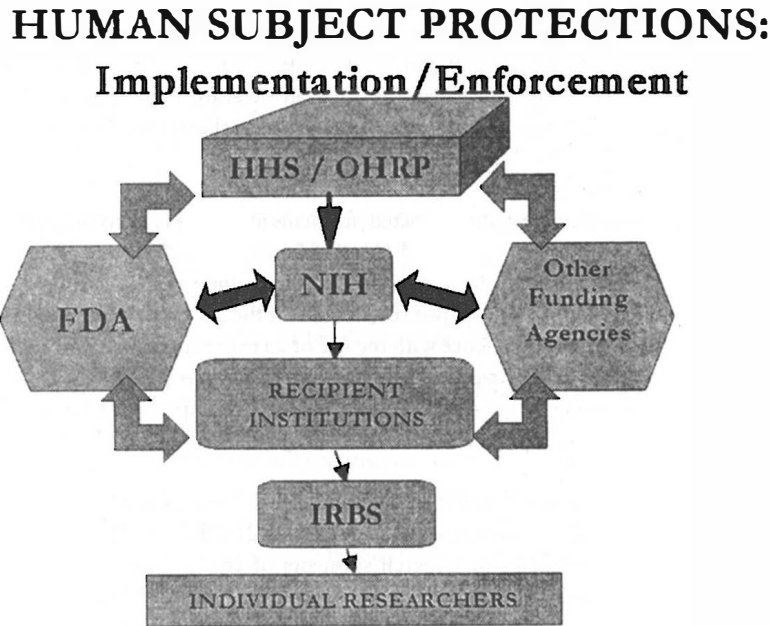
59. See IRB REFERENCE BOOK, *supra* note 53, at 20-21.

60. *Id.* at 20. See NAT'L BIOETHICS ADVISORY COMM'N, ETHICAL AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS (May 18, 2001), at <http://bioethics.gov/press/finalrecomm5-18.html> (last visited Sept. 4, 2001) (proposing establishment of a single, independent federal office to implement a unified, single set of regulations and guidance).

61. See 45 C.F.R. § 46.101 (2000) (referring to DHHS protection for human subject regulations); 21 C.F.R. § 50.20 (2001) (referring to FDA informed consent regulations). See also DEP'T OF HEALTH & HUMAN SERVS., OFFICE FOR HUMAN RESEARCH PROTECTIONS, COMPLIANCE OVERSIGHT PROCEDURES (2000) [hereinafter COMPLIANCE OVERSIGHT PROCEDURES], at <http://www.ohrp.osophs.dhhs.gov/compovr.htm> (last visited Aug. 23, 2001). See generally 21 C.F.R. pt. 56 (2001). The FDA also has additional regulations pertaining to Investigational New Drug Applications. 21 C.F.R. § 600.3 (2001). See generally 21 C.F.R. pt. 312 (2001); 21 C.F.R. pt. 812 (2001); BIOTECHNOLOGY, *supra* note 2, at ch. 9.

62. IRB REFERENCE BOOK, *supra* note 53; BIOTECHNOLOGY, *supra* note 2, at ch. 9. See also Jeffrey L. Fox, *Sweeping Bioethical Reform Proposals Contemplated for Trials*, 18 NATURE BIOTECHNOLOGY 1237 (2000).

Common Rule,⁶³ delegate responsibility to recipient institutions, charging them with establishing institutional review boards (IRBs) for review of individual research protocol proposals. This regulatory regime is illustrated in figure 2.



(Figure 2)

The net effects of this regime are the dual protections of informed consent and IRB review.⁶⁴ IRBs and the researchers they oversee are accountable for a

63. See generally IRB REFERENCE BOOK, *supra* note 53; BIOTECHNOLOGY, *supra* note 2, at ch. 9.

64. Exemptions from the dual protections of informed consent and IRB review, as set forth under 45 C.F.R. § 46.101(b) (2000), are restricted to research activities in which human subject involvement is limited to one or more of the following categories: (a) research on instructional techniques, curricula, or classroom management methods conducted in established educational settings; (b) research on the use of educational tests and survey and interview procedures, unless subjects can be identified and disclosure could put the subjects at risk; (c) research on the use of educational tests and survey and interview procedures if the subjects are public officials candidates for public office, or the confidentiality of personally identifiable information is protected by statute; (d) research involving the collection or study of existing data or specimens which are publicly available or not identifiable; (e) research to evaluate the effectiveness of agency programs; and (f) taste and food quality evaluations where ingredients are deemed safe by a federal agency. 45 C.F.R. § 46.101(b). See IRB REFERENCE BOOK, *supra* note 53, at 65-67. FDA also exempts certain clinical investigations from IRB requirements—for example, an investigation involving emergency use of a test article when the emergency is reported to an IRB within five working days. See 21 C.F.R. §

myriad of review and reporting requirements.⁶⁵ Nevertheless, IRBs are comprised

56.104(c)-(d) (2001). Moreover, FDA is authorized to waive the IRB requirement for specific research activities. *See* 21 C.F.R. § 56.105 (2001). *See also* IRB REFERENCE BOOK, *supra* note 53, at 65-67. For guidance on implementation of these regulations, OPRR (predecessor to OHRP) has provided the decision trees reproduced as Figure 9-1.1 and Figure 9-1.2. These decision trees and additional guidance are available at Office for Human Research Protections, DHHS, at <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/decisioncharts.htm> (last visited Sept. 4, 2001).

65. These requirements include:

- Prompt reporting of any unanticipated problems involving risks to subjects or others. *See* 45 C.F.R. § 46.103(b)(5) (2000); 21 C.F.R. § 56.108(b)(1) (2001).
- Notification (a) to the FDA by facsimile or other writing as soon as possible, no later than seven calendar days, of the sponsor's receipt of the information of any unexpected fatal or life-threatening experience with the use of an experimental drug or biologic; and (b) to the FDA and all participating investigators as soon as possible, no later than 15 calendar days, after the sponsor determines that use of an experimental drug or biologic is both serious and unexpected. *See* 21 C.F.R. § 312.32(c)(1)-(2) (2001); 21 C.F.R. § 312.64(a)-(b) (2001).
- Sponsor notification to clinical investigators of all "new observations," particularly those pertaining to adverse effects and safe use. *See* 21 C.F.R. § 312.55 (2001).
- Investigator notification to research sponsors of any adverse effects that may be reasonably regarded as being caused by the drug. *See* 21 C.F.R. § 312.64(b) (2001).
- Investigator notification within ten working days to sponsors and overseeing IRBs of any unanticipated adverse effects. *See* 21 C.F.R. § 812.46(b) (2001). In turn, within ten days of receiving the information, sponsors must evaluate the event and report to the FDA, all participating investigators, and all reviewing IRBs. *See* 21 C.F.R. § 812.46(c) (2001).

Although the FDA does not currently require IRB registration, all IRBs and Institutional Ethics Committees (IECs) operating in conjunction with an OHRP Federal-wide Assurance of Protection for Human Subjects must register with DHHS. *See* Office for Human Research Protections, IRB Registration and Assurance Filing Procedures General Information, at <http://ohrp.osophs.dhhs.gov/humansubjects/assurance/refinfo.htm> (last visited Sept. 4, 2001). Other IRBs and IECs are encouraged to register voluntarily to facilitate effective communication with DHHS. *See id.*

In addition, federal regulations mandate that IRBs embody the expertise necessary to review the variety of research the IRB will review, are sufficiently knowledgeable of human subject regulations, and practice impartiality. *See* 21 C.F.R. § 56.107(a) (2001); IRB REFERENCE BOOK, *supra* note 53, at 84. The regulations also stipulate that IRBs consist of at least five members and be professionally, culturally, and racially diverse and gender balanced. *See* IRB REFERENCE BOOK, *supra* note 53, at 85-86. Each IRB must have at least one member whose primary concerns are in non-scientific areas, and at least one non-scientist member must be present for an IRB to conduct business at convened meetings. *See id.* at 86.

Federal regulations also impose an obligation on recipients of National Institutes of Health (NIH) funding to receive sufficient education about the protection of human subjects. *See* NAT'L INST. OF HEALTH, GUIDELINES FOR THE CONDUCT OF RESEARCH INVOLVING HUMAN SUBJECTS AT THE NATIONAL INSTITUTES OF HEALTH (revised Mar. 2, 1995), at <http://>

of members who volunteer their time, the majority of which are drawn from the institution's own community and are colleagues of those submitting protocols for IRB approval.⁶⁶ Criticisms of the IRB system, especially after they were documented in a four-part report issued by the Office of Inspector General in 1998, have become well-known: (1) IRBs are overwhelmed and, therefore, often take short-cuts in their review—e.g., making decisions on research proposals without the full committee; (2) IRBs often lack the necessary expertise to adequately review specific protocols; (3) IRBs are subject to institutional and peer pressures, and (4) after approval, IRBs often are lax in ongoing oversight⁶⁷—meaning that IRBs have virtually no contact with human subjects or researchers once research is underway.⁶⁸

ohsr.od.nih.gov/guidelines.php3 (last visited Sept. 4, 2001). Investigators who submit funding applications must describe the relevant education of key personnel, which includes "all individuals responsible for the design and conduct of the study and include graduate students, technicians, research associates and other professionals." IRB REFERENCE BOOK, *supra* note 53, at 87. Moreover, OHRP has recently emphasized the obligation of institutions to provide IRB operational support sufficient to satisfy federal obligations, and OHRP has cited institutions for insufficiently supporting their IRB and human subject protection operations. See generally COMPLIANCE OVERSIGHT PROCEDURES, *supra* note 61.

66. To meet competency requirements mandated under federal law, IRBs may invite individuals with special expertise to assist in reviewing specific issues, but such consultants may not vote with the IRB. See IRB REFERENCE BOOK, *supra* note 53, at 86. Research institutions also may turn to commercial or independent IRBs and enter into agreements with other institutions to use their IRB review process. See *id.* at 84-85. In fact, the latter may be an emerging trend.

The Office for Human Research Protection (OHRP) has recently approved an innovative approach for multiple institutions that are working collectively on research. The Multicenter Academic Clinical Research Organization (MACRO) is a unique partnership of five leading academic centers with a reciprocal IRB approval process. One of the five university IRBs is designated as the IRB of record for each collaborative. Once the designated IRB approves the research, review by the IRBs at the other four MACRO institutions is unnecessary.

Id. at 85.

67. Moreover, IRBs are required to engage in continuing review of research, including review of investigator requests for study changes, and a meaningful review not less than once per year. See 45 C.F.R. § 46.109(e) (2000); 21 C.F.R. § 56.109(f) (2001). IRBs are authorized to engage in post-approval reviews at intervals of less than one year to reflect levels of risk, and are required to provide written guidance on how they will make these risk-review assessments in their Standard Operating Procedures. See 45 C.F.R. § 46.103(b)(4)(ii) (2000).

68. See generally IRB REFERENCE BOOK, *supra* note 53; DEP'T HEALTH & HUMAN SERVS., INSTITUTIONAL REVIEW BOARDS: A TIME FOR REFORM, PUB. NO. OEI-01-97-00193 (1998); DEP'T HEALTH & HUMAN SERVS., INSTITUTIONAL REVIEW BOARDS: THEIR ROLE IN REVIEWING APPROVED RESEARCH, PUB. NO. OEI-01-97-00190 (1998) [hereinafter ROLE IN REVIEW]; DEP'T HEALTH & HUMAN SERVS., INSTITUTIONAL REVIEW BOARDS: THE EMERGENCE OF INDEPENDENT BOARDS, PUB. NO. OEI-01-97-00192 (1998); DEP'T HEALTH & HUMAN SERVS.,

Even given these weaknesses in the regulatory regime to protect human subjects, the regime's lack of reliability as a safeguard against conflicts of interest is largely attributable to a failure to exercise existing oversight authority. The DHHS (including OHRP, NIH, and the FDA) holds broad jurisdiction over clinical research—meaning there is ample jurisdictional latitude for enforcement of conflicts standards and regulatory reform.⁶⁹

C. Complementary Weaknesses in Conflicts Regulations

Meaningful avoidance and management of conflicts of interest presupposes that institutions have full and ongoing knowledge of their technology transfer and human subject research activities, including those undertaken through collaborations. However, as discussed above, the reality is a ridiculously low level of accountability, which now is being acknowledged by the institutions themselves⁷⁰ and NIH in the context of opposing the imposition of additional conditions on the commercialization of government-sponsored research.⁷¹ The convergence of clinical research and clinical care⁷² exacerbates concerns.

Existing conflicts-of-interest regulations simply complement the technology transfer and human subject protection regulatory schemes, and shadow their weaknesses by relying heavily upon self-compliance by institutions and researchers who are funding recipients.⁷³ Although federal regulations mandate the disclosure of financial interests by individuals who apply to the Public Health Service (PHS)⁷⁴ and the National Science Foundation (NSF) for research funding,⁷⁵ these regulations are limited in scope.⁷⁶ For example, PHS and NSF

INSTITUTIONAL REVIEW BOARDS: PROMISING APPROACHES, PUB. NO. OEI-01-91-00191 (1998); Symposium: *Human Subjects Research and the Role of Institutional Review Boards—Conflicts and Challenges*, 28 J. AM. SOC'Y L. MED. & ETHICS 329 (2000).

69. See Fox, *supra* note 62; Rose, *supra* note 57. For example, the FDA is authorized to review IRBs, clinical investigators, research sponsors, and institutional oversight of both clinical and animal laboratories. See 21 C.F.R. § 56.115(b) (2001); 21 C.F.R. § 312.68 (2001). The FDA may require IRBs and their institutions to: (a) withhold approval of new studies; (b) prohibit the enrollment of new subjects; (c) terminate ongoing studies; (d) notify other agencies of institutional noncompliance; and (e) for serious noncompliance, even disqualify an IRB. See 21 C.F.R. § 56.120(b) (2001); 21 C.F.R. § 56.120(a) (2001). See also IRB REFERENCE BOOK, *supra* note 53, at 307.

70. Carey Goldberg, *Medical Schools Offer Rules on Doctors' Conflict of Interest*, N.Y. TIMES, Feb. 8, 2001, at A23. Several top schools, including Harvard, "are proposing stringent conflict-of-interest guidelines for doctor-researchers who have financial stakes in their work." *Id.*

71. See generally NIH RESPONSE, *supra* note 21.

72. See *supra* Part II.

73. For a thorough, technical treatment of the regulatory regime, policy statements, and professional standards for financial conflicts of interest, see generally Rose, *supra* note 57.

74. See Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding is Sought, 42 C.F.R. §§ 50.601-50.607 (2000). These regulations date back to 1995. *Id.*

75. See Rules of Practice for the National Science Foundation, 45 C.F.R. §§ 680.10-680.13

regulations exclude equity interests having a fair market value of less than \$10,000 and that do not constitute an ownership interest greater than five percent in any single entity.⁷⁷ The regulations also exclude regular salaries paid by the application institution, royalties paid by the application institution, honoraria paid for service to public or non-profit groups, and salaries, royalties, and honoraria from private and for-profit groups, provided that total payments do not exceed \$10,000 over a twelve-month period.⁷⁸ Similarly, the reporting threshold under FDA regulations is \$25,000 in excess of the documented costs of conducting the research or clinical trial.⁷⁹ The FDA regulations prohibit investigators from having financial interests in the technologies they are testing beyond those disclosed and deemed allowable.⁸⁰

To implement these requirements, PHS regulations require applicant institutions to maintain and enforce written conflict of interest policies, to inform investigators about these policies and PHS regulations, to appoint an institutional official to collect and evaluate financial disclosure statements from investigators before the institution applies for PHS funding, and to maintain sufficient records.⁸¹ FDA regulations hold investigators responsible for making requisite disclosures directly to the FDA.⁸² Nevertheless, under these regulations, individuals only have to report financial interests related to the research proposal for funding, and make this disclosure only to institutional officials or directly to the FDA—meaning not publicly, and not even to the subjects in their studies.⁸³

(2000).

76. Clarification is available at Frequently Asked Questions Concerning the Department of Health and Human Services Objectivity in Research Regulations and the National Science Foundation Investigator Financial Disclosure Policy, 61 Fed. Reg. 34,839 (July 3, 1996). *See also* Rose, *supra* note 57.

77. 42 C.F.R. § 50.603(1), (3)-(5) (2000).

78. *See id.*; 21 C.F.R. §§ 54.1-54.6 (2001); FOOD & DRUG ADMIN., DRAFT: GUIDANCE FOR INDUSTRY: FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS (Oct. 26, 1999).

79. These regulations were finalized in 1998, took effect in February 1999, and subsequently have been clarified by draft guidance published in October 1999 and finalized on March 28, 2001. *See* FOOD & DRUG ADMIN., DEPT HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS (2001) [hereinafter FDA GUIDANCE], at <http://www.fda.gov/oc/guidance/financialdis.html> (last visited Sept. 4, 2001).

80. *See id.* The regulations also require general investigator disclosure of financial interests exceeding \$50,000 in any publicly held company. 21 C.F.R. §§ 54.1-54.6 (2001).

81. *See* 42 C.F.R. § 50.604(a)-(c) (2000); 42 C.F.R. § 50.603 (2000). Institutions are required to certify these conflict of interest policies and procedures with the Public Health Service. *See* 42 C.F.R. § 50.604(g)(1) (2000).

82. *See* FDA GUIDANCE, *supra* note 79. These disclosures must be made while the study is ongoing and within one year after completion. *See id.*

83. *See generally* Korn, *supra* note 25, at 2236; Cho, *supra* note 12. The FDA has provided reassurances that financial information about investigators will be disclosed publicly only in instances where a public interest in disclosure clearly outweighs an individual researcher's privacy

Unfortunately, the majority of U.S. research institutions have not even risen to the occasion of generating sufficient conflicts of interest guidelines. "Most policies on conflict of interest at major US research institutions lack specificity about the kinds of relationships with industry that are permitted or prohibited."⁸⁴ This fact is even more troubling when considered in light of the absence of technology transfer auditing and reliable information management by funding agencies, as readily acknowledged by NIH in defense of the United States' aggressive technology transfer policy.⁸⁵

D. Implications for Clinical Research

The human health benefits of making breakthrough products—especially those for life-threatening and presently untreatable conditions—accessible to patients prior to full market approval may be beyond question at this time due to the prolific state of biomedical research.⁸⁶ Nevertheless, the present regulatory regime for protecting human subjects is unreliable in general,⁸⁷ and certainly

interests. *See generally* FDA GUIDANCE, *supra* note 79.

In the U.S., the reasonable-physician standard, which is applied from the provider's perspective and rests on medical judgment, gradually has been replaced by a material-risks standard. Under the latter, the boundaries of the disclosure rest on the individual patient's need to know, not on prevailing and somewhat paternalistic medical standards.

BIOTECHNOLOGY, *supra* note 2, at § 9.03[B][1]. Written consent forms for non-FDA-approved drugs should provide subjects with the information necessary to enable them to calculate their own risk-to-benefit ratio. *See id.* at § 9.03[B][2]. Relevant regulations mandate that consent forms include eight basic elements, with potentially six additional subparts for research involving more than minimal risk. *See* 45 C.F.R. § 46.116(a) (2000); 21 C.F.R. § 50.25(a) (2001). *See also* IRB REFERENCE BOOK, *supra* note 53, at 164-168. Moreover, the regulations expressly state that the forms must not contain language that could be considered exculpatory. *See* 45 C.F.R. § 46.116 (2000); 21 C.F.R. § 50.20 (2001).

Exculpatory language is described in the regulations as language through which the subject or the subject's representative is made to waive or appear to waive any of the subject's legal rights or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

IRB REFERENCE BOOK, *supra* note 53, at 163. OHRP recently issued further relevant guidance. *See* OFFICE OF HUMAN RESEARCH PROTECTIONS, DRAFT INTERIM GUIDANCE: FINANCIAL RELATIONSHIPS IN CLINICAL RESEARCH: ISSUES FOR INSTITUTIONS, CLINICAL INVESTIGATORS, AND IRBS TO CONSIDER WHEN DEALING WITH ISSUES OF FINANCIAL INTERESTS AND HUMAN SUBJECT PROTECTION (2001) [hereinafter OHRP DRAFT GUIDANCE], at <http://ohrp.osophs.dhhs.gov/humansubjects/finreltn/finguid.htm> (last visited Aug. 23, 2001).

84. Cho, *supra* note 12, at 2208.

85. *See* NIH RESPONSE, *supra* note 21, at pt. E.

86. *See generally supra* note 1 and accompanying text.

87. *See supra* Part III. A.

unreliable as a mechanism to police against conflicts of interest.⁸⁸ Integrating clinical research and clinical care means folding the ridiculously low level of reliable institutional accountability associated with technology transfer and human subjects protection into delivery of care.⁸⁹ A likely consequence, and one difficult to measure given the present lack of institutional accountability,⁹⁰ is exacerbation of the prevalence of conflicts of interest that endanger research integrity and the protection of human subjects.

The situation is still further complicated by the fact that the delivery of care system and the physicians working within that system are squeezed financially by managed care.⁹¹ Moreover, increasingly today's trials involve a collection of institutions and transcend borders.⁹² With commercial demand for research subjects at an all-time high,⁹³ physicians and their institutions have the opportunity to reap extraordinary financial returns by becoming subject

88. For a summary of the oversight mechanisms for clinical research, see Ralph Snyderman & Edward W. Holmes, *Oversight Mechanisms for Clinical Research*, 287 *SCIENCE* 595, 595-97 (2000).

89. For a discussion of the accountability problem (i.e., over-reliance on over-burdened IRBs and self-policing by funding recipients in the absence of reliable technology transfer information management and auditing by government sponsors and recipient institutions), see generally *supra* Part III; NIH RESPONSE, *supra* note 21.

90. See *supra* note 89.

91. See generally Kenneth E. Thorpe et al., *The Impact of HMOs on Hospital-Based Uncompensated Care*, 26 *J. HEALTH POLS. POL'Y & L.* 543, 544-46 (2001); KENNETH M. LUDMERER, *TIME TO HEAL: AMERICAN MEDICAL EDUCATION FROM THE TURN OF THE CENTURY TO THE ERA OF MANAGED CARE* (1999).

92. U.S. policy to protect human subjects applies to research conducted in foreign countries. See 45 C.F.R. § 46.101(a) (2000). Therefore, human subjects outside the U.S. must be allotted the dual protection of informed consent and IRB review. See IRB REFERENCE BOOK, *supra* note 53, at 340. However, the regulations also embody the possibility of deference to host-country regimes. When host countries have implemented protections equivalent to U.S. protections, a "department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy." 45 C.F.R. § 46.101(h). Data and Safety Monitoring Boards (DSMB) are required for multi-site clinical trials that entail potential risk to participants. See 45 C.F.R. § 46.111(a)-(b) (2000); DEP'T HEALTH & HUMAN SERVS.: International Conference on Harmonisation; Good Clinical Practice Consolidated Guideline, 62 Fed. Reg. 25,692, 25,701 (May 9, 1997); IRB REFERENCE BOOK, *supra* note 53, at 286. This oversight is distinct from IRB study review and approval requirements. *Id.* at 287.

93. Microarray (e.g., DNA chip) and bioinformatics capabilities are raising the utility of—meaning the amount of useful information that can be derived from—and demand for subject samples to an all-time high. Cf. *Snake Oil*, *supra* note 3. However, information technology is being developed with the goal of simulating the effect of new drugs on cells, organs, and systems in the human body before clinical testing, thereby potentially streamlining clinical trials. See *IBM/Physiome Sign Supercomputing of Biological Modeling Pact*, MAINFRAME COMPUTING (Oct. 1, 2001), available at 2001 WL 12586424 (reporting that IBM's supercomputing technology will be used for biomedical research).

suppliers.⁹⁴ Pressing issues in subject recruitment, given the intensely competitive environment for contemporary biomedical R&D, include the payment of recruitment incentives for investigators,⁹⁵ compensation to subjects,⁹⁶ use of medical records,⁹⁷ and internet recruitment.⁹⁸ The potential for non-financial conflicts of interest is equally troubling given the present state of competition in biomedical research and demand for research subjects.⁹⁹

94. Cf. Frances H. Miller, *Trusting Doctors: Tricky Business When It Comes to Clinical Research*, 81 B.U. L. REV. 423 (2001). Although the American Medical Association and other professional associations prohibit referral fees, the practice is common to the extent that sponsors often "reimburse" referring physicians generously for administrative and other expenses. See MEDICARE REIMBURSEMENT IN CLINICAL TRIALS, *supra* note 1, at 41-42. For example, based upon data available in 1996, in oncology research physicians are paid \$2,500 per patient for industry-sponsored trials and \$750 per patient from the National Cancer Institute. See *id.* Compensation may also take many other forms, such as honoraria for speaking engagements, paid consulting and advisory positions, and even equity interests. See Boyd & Bero, *supra* note 8, at 2211.

95. See *supra* note 94.

96. It is common practice for sponsors and even research institutions to compensate subjects for participating in research. "Financial incentives are often used in the early phases of investigational drug, biologic, or device development, especially when health benefits to subjects are inconsequential or non-existent." IRB REFERENCE BOOK, *supra* note 53, at 228. Given that monetary compensation raises questions about subject coercion and compensation to providers and their affiliated institutions introduces potential conflicts of interest, institutions should set clear, specific policy on compensation and disclosure even indirectly associated with subject recruitment. See *id.* IRBs should carefully review proposed recruitment methods and imposed elevated standards of disclosure to subjects as part of the informed consent process. See *id.* at 224.

97. Traditionally, investigators have used medical records to identify and recruit potential research subjects. IRB REFERENCE BOOK, *supra* note 53, at 226. However, that national attention placed on medical privacy and implementation of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), 45 C.F.R. § 160 have brought many of these medical record review practices into question.

98. An alternative to use of medical records that is being aggressively pursued is direct communication with subjects via advertisements and posting Internet information about trials. See *supra* note 96. Generally, the FDA treats Internet postings and advertisements in a similar fashion: postings with minimal information do not require IRB review. See FOOD & DRUG ADMIN., INFORMATION SHEETS, GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS AND CLINICAL INVESTIGATORS, 1998 UPDATE, at <http://www.fda.gov/oc/ohrt/irbs/toc4.html> (last visited Sept. 4, 2001). "Conversely, if additional descriptive information is listed on the Internet, IRB review and approval may ensure that the additional information does not promise or imply benefits beyond what is indicated in the protocol and the informed consent documents." IRB REFERENCE BOOK, *supra* note 53, at 227.

99. See Kuszler, *supra* note 25, at n.180 and accompanying text.

IV. PROPOSALS FOR REFORM

Contemporary financial conflicts of interest are not simply an extension of the longstanding non-financial conflicts which have been pervasive for years, and clinical research is readily distinguishable from basic research in light of the additional human health concerns and bioethical complications.¹⁰⁰ As discussed throughout this article, academia and industry have integrated and the unprecedented pace of scientific advancement and demand for human subjects place extraordinary pressures on researchers and their institutions.¹⁰¹

However, academia and industry have integrated and there is no turning back, nor should that be considered a desirable policy option.¹⁰² The health science community has never been so productive and offered as much promise to patients in need.¹⁰³ The policy objective should be to introduce the level of institutional assurance necessary to allow life science to move forward with all the collaborative synergies that have advanced the field and improved health care thus far.

Options include maintaining but building upon the present regulatory methodology—i.e., relying heavily upon self-regulation by institutions and professional societies. In fact, responsive self-regulation initiatives are already underway. First, representatives from several of the nation's top medical schools (Harvard, Baylor College of Medicine, Columbia University, Johns Hopkins University, the University of Pennsylvania, the University of Washington, Washington University, Yale University, and the University of California at San Francisco and Los Angeles) have jointly drafted conflicts of interest guidelines requiring researchers to disclose any financial interests they have in studies involving patients.¹⁰⁴ Second, rather than continuing to rely on IRBs to manage conflicts issues, some institutions have established conflicts committees.¹⁰⁵ This approach introduces an administrative mechanism centered on conflicts rather than further over-extending the already overwhelmed IRB system, which has the broad mission of protecting human subjects.¹⁰⁶ Third, several major professional societies have introduced responsive guidelines. For example, the American

100. See Korn, *supra* note 25, at 2234-35 (distinguishing contemporary financial conflicts of interest from more familiar and pervasive conflicts—i.e., a bias toward positive research results—that have generated traditional management mechanisms).

101. See generally *supra* Part I.

102. See generally NIH RESPONSE, *supra* note 21. But see *Regulating Scientific Research*, *supra* note 8.

103. See *supra* notes 1-7 and accompanying text.

104. See also Katherine S. Mangan, *Medical Schools Draft Guidelines for Preventing Conflicts of Interest*, CHRON. HIGHER EDUC., Feb. 23, 2001, at A36; Goldberg, *supra* note 70. See also *infra* note 114.

105. See *infra* notes 115-16 and accompanying text.

106. See ROLE IN REVIEW, *supra* note 68. See generally IRB REFERENCE BOOK, *supra* note 53; *supra* notes 43-44 and accompanying text.

Society of Gene Therapy has prohibited researchers from taking equity interests in companies sponsoring trials they run,¹⁰⁷ and the Association of American Medical Colleges (AAMC) has announced assembling a task force on conflicts of interest issues.¹⁰⁸ The American Medical Association (AMA) has adopted a policy on conflicts of interest calling on all medical centers to develop guidelines that embody stipulations to avoid perceived as well as actual conflicts in order to maintain public trust as well as scientific objectivity and integrity.¹⁰⁹

Another option is to raise agency standards and enforcement. Along these lines, in June 2000, former Secretary of DHHS Donna Shalala replaced the Office for Protection from Research Risks (OPRR), which was located within NIH, with OHRP.¹¹⁰ OHRP is situated within the Office of the Secretary.¹¹¹

Moreover, on May 23, 2000, then Secretary Shalala announced initiatives to expand protections for clinical trial participants, including a NIH clarification of conflict of interest rules for federally funded researchers and a promise to host public discussion on conflicts of interest management.¹¹² These reforms also included proposals to enhance the FDA's oversight role with additional enforcement capabilities such as levying significant sanctions and financial

107. See AMER. SOC'Y OF GENE THERAPY (ASGT), POLICY OF THE AMERICAN SOCIETY OF GENE THERAPY ON FINANCIAL CONFLICT OF INTEREST IN CLINICAL RESEARCH (2000), at <http://www.asgt.org/policy/index.html> (last visited Sept. 4, 2001).

108. Present AAMC guidelines, in place since 1990, recognize that conflicts of interest are inevitable and emphasize the need to manage conflicts of interest. See ASS'N AMER. MED. COLLEGES, GUIDELINES FOR DEALING WITH FACULTY CONFLICTS OF COMMITMENT AND CONFLICTS OF INTEREST IN RESEARCH (1990), at <http://www.aamc.org/research/dbr/coi.htm> (last visited Sept. 4, 2001). See Rose, *supra* note 57, at n.29 and accompanying text.

109. See generally AM. MED. ASS'N, COUNCIL ON ETHICAL & JUDICIAL AFFAIRS, CONFLICTS OF INTEREST: BIOMEDICAL RESEARCH, Op. E-8.031 (1999), at <http://www.ama-assn.org/ama/pub/category/2503.html> (last visited Aug. 15, 2001). The AMA calls for implementation of guidelines that embody the following stipulations:

- Investigator cannot buy or sell company stock while involved with said company's research and until research results are publicly disclosed.
- Compensation to investigators must be commensurate with efforts.
- Investigators must disclose relevant financial and other interests in the research sponsor, in writing, to the relevant medical center and funding organizations. In addition, COI disclosure must accompany any journal submissions.

Id.

110. See IRB REFERENCE BOOK, *supra* note 53, at 21.

111. See *id.*

112. Press Release, Department of Health and Human Services, Secretary Shalala Bolsters Protections for Human Research Subjects (May 23, 2000) [hereinafter DHHS Press Release], available at <http://www.hhs.gov/news/press/2000pres/20000523.html>; Donna Shalala, *Protecting Research Subjects—What Must Be Done*, 343 NEW ENG. J. MED. 808, 809 (2000). As a result of these public forums, NIH and FDA are expected to develop joint conflicts of interest policies. See Rose, *supra* note 57, at 8.

penalties against researchers and institutions.¹¹³ Another proposal was to require institutions, academic sponsors, and agencies to utilize and share data resulting from safety monitoring boards.¹¹⁴ In addition, during the summer of 2000, NIH undertook "visits" to recipient institutions throughout the country to see first-hand how these institutions are dealing with conflicts of interest.¹¹⁵

To advance meaningful reform, in June 2000, DHHS also chartered a National Research Human Protection Advisory Committee (NRHPAC) to consult with both the Secretary and OHRP on issues related to the protection of human subjects.¹¹⁶ OHRP has now issued a draft guidance encouraging institutions to establish conflicts committees expressly responsible for conflict of interest management.¹¹⁷ As proposed by OHRP, these committees would be responsible for collecting and evaluating information about financial relationships between commercial sponsors, investigators, IRB members and staff. These committees also will assess potential institutional conflicts of interest in a proactive manner.¹¹⁸ More recently, on March 28, 2001, the FDA issued a final Guidance for Industry on Financial Disclosure by Clinical Investigators.¹¹⁹ This guidance constitutes the FDA's response to the deluge of questions the agency received in response to its final regulations.¹²⁰

The Bush Administration should establish the Bioethics Advisory Committee announced in August, 2001, and then embrace the spirit of comprehensive reform associated with the enactment of federal technology transfer legislation and the modernization of the FDA, which triggered the explosion in life science that has now reached the clinic.¹²¹ Too much reliance has been placed on research institutions for far too long.¹²² Both public and private research

113. See Rose, *supra* note 57, at 12-14.

114. See *id.* These boards are required for multi-site clinical trials that entail potential risk to participants. See 45 C.F.R. § 46.111(a)-(b) (2000). In June 2000, NIH issued guidance on data and safety monitoring for Phase I and Phase II clinical trials. See NAT'L INST. OF HEALTH, FURTHER GUIDANCE ON A DATA AND SAFETY MONITORING FOR PHASE I AND PHASE II TRIALS, Notice OD-00-038 (June 5, 2000), at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html> (last visited Sept. 4, 2001).

115. See Patrick Healy, *Harvard Forum Eyes Oversight of Biomedical Research*, BOSTON GLOBE, July 21, 2000, at A13.

116. See Rose, *supra* note 57, at 15-16.

117. See generally OHRP DRAFT GUIDANCE, *supra* note 83.

118. See *id.*

119. See FDA GUIDANCE, *supra* note 79.

120. See *id.*

121. See generally NIH RESPONSE, *supra* note 21; GAO REPORT, *supra* note 8.

122. See generally Cho, *supra* note 12. According to a recent study, Harvard Medical School is the only major academic institution to have established absolute limits on faculty financial interests in their research. See Bernard Lo, et al., *Conflict-of-Interest Policies for Investigators in Clinical Trials*, 343 NEW ENG. J. MED. 1616, 1618-19 (2000). Harvard faculty must not hold more than \$20,000 in stock or receive more than \$10,000 in consulting fees and research royalties from sponsors. See *id.*

institutions, as the recipients of vast amounts of public funding and even more trust, should be subjected to enforced standards of academic disclosure in the spirit of the rigorous investor disclosure associated with small, publicly traded companies.

Continuing with the initiatives undertaken by former Secretary Shalala, the Bush Administration must implement meaningful assurance that conflicts of interest (which are pervasive now and will become even more pervasive as biomedical research moves forward) will not jeopardize the rights of human subjects or research integrity. Institutions have embraced opportunities to collaborate introduced under Bayh-Dole, but the institutions have moved forward without proper reflection and without taking needed proactive administrative measures to ensure accountability.¹²³

First, uniform, workable, and enforceable federal conflicts of interest standards should be directly written into federal technology transfer policy¹²⁴ and implemented in a parallel fashion by all DHHS agencies. The standards themselves should be specific enough to minimize subjective interpretation. Further, they should err on the side of disclosure, albeit in a manner sensitive to commercial interests—which is a principle already embodied in federal technology transfer policy via the invention reporting provisions and FDA policies.¹²⁵ As an immediate measure, NIH technology transfer guidelines should be enhanced and made requirements for recipient institutions.¹²⁶ To make this approach enforceable, the federal government must immediately implement the information management mechanisms essential to trace and account for the public's investment in biomedical research from the bench to market.¹²⁷

Second, the same institutions that presently are relied upon to comply with human subjects protection regulations and technology transfer reporting requirements should be subject to mandatory disclosure and compliance audits. For example, NIH has required safety monitoring boards for many types of large

In spite of competitive pressures such as retention of faculty, Harvard recently decided to adhere to this standard. See Katherine S. Mangan, *Harvard Medical School Will Keep Its Conflict-of-Interest Policies*, CHRON. HIGHER EDUC., June 9, 2000, at A36; Richard A. Knox, *Harvard Won't Ease Research Standards: Medical School Stands by Conflict Rules*, BOSTON GLOBE, May 26, 2000, at A1. Moreover, Harvard is demonstrating caution in its dealings with Merck & Co., which was the first major drug company to establish a facility at Boston's Longwood Medical Area. See Liz Kowalczyk, *Harvard To Use Caution with Merck: Dean Says Med School Won't Pursue a Major Licensing Pact with Firm*, BOSTON GLOBE, Aug. 1, 2001, at C1. Harvard will pursue a series of technology-specific collaborations with Merck, rather than a broad, multimillion-dollar deal. See *id.*

123. See Cho, *supra* note 12, at 2208. See generally *supra* Part III. A.

124. See *supra* note 11 (identifying relevant legislation).

125. See *id.* See also *supra* note 83 and accompanying text.

126. See Objectivity in Research, 59 Fed. Reg. 33,242 (June 28, 1994).

127. See generally NIH RESPONSE, *supra* note 21.

clinical trials,¹²⁸ but NIH has not forced prompt disclosure, such as industry sponsor disclosure to the IRBs, of academic collaborators.¹²⁹

Through such enhanced standards backed by meaningful enforcement, the institutions engaged in clinical research will be compelled to finally implement meaningful accountability measures. Presumably, such measures would include administratively bridge grant management and technology transfer, the appointment of compliance officers, and engagement in routine technology transfer self-audits. Such basic measures are essential to ensure that grant recipient researchers, their departments, and the institutions themselves are avoiding conflicts of interest and, to the extent that conflicts prove unavoidable, managing them responsibly.

V. CONCLUSION

The world around institutions engaged in clinical research has changed. To one side, basic research has become focused on application, and industry and academia have fully integrated. To the other, clinical research and clinical care are converging and clinical research has become dominated by a global CRO industry.

Conflicts of interest are institutional weeds. They take root below the surface and become pervasive problems often long before they show their ugliness. In health care, that ugliness includes incidents such as the death of gene therapy patient Jesse Gelsinger,¹³⁰ as well as the recent law suit by Immune Response against researchers at Harvard and the University of California.¹³¹

Public confidence in clinical trials is very high, evidenced by the demand for information about and access to trials, and general willingness to participate. That trust must not be lost. Rather, we must recognize that the role of institutions has changed and implement needed federal oversight changes so that we can embrace the benefits of the change, maintain the public's trust in health science, and move forward with the mission of improving human health.

128. See *supra* note 114.

129. See DHHS Press Release *supra* note 112.

130. See *supra* note 40 and accompanying text.

131. See *supra* note 41 and accompanying text.