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Financing Clinical Research and Experimental Therapies: Payment Due, But From Whom?

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FINANCING CLINICAL RESEARCH AND EXPERIMENTAL THERAPIES: PAYMENT DUE, BUT FROM WHOM?

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INTRODUCTION

We live in the age of the possible. It is possible to implant the organ of a cadaver into the chest of the dying man restoring him to a vigorous life with a better beating heart.[1] It is possible to destroy the blood-making marrow of the cancer patient with a near lethal dose of chemotherapy, and then rescue her with saved or donated marrow.[2] And it is possible to tailor a virus to deliver a gene loaded with instructions for making a missing enzyme to a patient who has a congenital deficiency.[3] But when do these miraculous possibilities merit the spending of scarce resources and ever more limited dollars?[4]

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[1]The first heart transplant was performed in 1967. Since then, the procedure has changed from a rare, arcane experiment to an established treatment received by approximately 2,300 persons every year. These people would almost certainly die were they not to receive a donor heart. *See* Facts about Heart and Heart-lung Transplants, <http://www.nhlbi.nih.gov/health/public/heart/other/hrt_lung.pdf>.

[2]*See* GAO/HEHS 96-83, Health Insurance—Coverage of Autologous Bone Marrow Transplantation for Breast Cancer, Apr. 24, 1996.

[3]*See* Joan Stephenson, *New Method to Repair Faulty Genes Stirs Interest in Chimeraplasty Technique*, 281 JAMA 119, 120 (1999). Sheryl Gay Stolberg, *Gene Patients Not Told All Facts Researchers Ignore Rules, FDA Says*, NEW ORLEANS TIMES-PICAYUNE, Jan. 27, 2000, at A1.

This question has been sidestepped with increasing frequency over the last two decades. Entranced with ever more sophisticated technology,[5] blessed with a propensity for medical innovation and unwilling to make difficult decisions,[6] the players in the drama of clinical research have had little, if any, incentive to draw the hard lines between that which merits funded investigation and that which is still unproven speculation.[7] Patients seek new treatments and aggressive interventions, arguing that even though unproven, they may provide a "last best chance" for a cure.[8] Researchers and physician providers eagerly advocate for the patients and the proposed therapy, sometimes without regard to quality and safety.[9] Health plans reluctantly pay for the experimental treatment, rather than being cast as villains in the courtroom of mass media.[10] Plans may pay out of ignorance or

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[4]*See* Timothy S. Jost, *Health Care Rationing in the Courts: A Comparative Study*, 21 HASTINGS INT'L & COMP. L. REV. 639, 644 (1998).

[5]"Americans love technology of any type. Much of this is justified and has led to our being a world leader in the manufacture and use of technology. It is deeply ingrained into our culture." Richard. D. Lamm, *The Ethics of Excess*, PUBLIC HEALTH REPORTS 218 (May-June 1996).

[6]*See* Ken Terry, *Technology: The Biggest Health-care Cost-driver of All*, MEDICAL ECONOMICS, Mar. 21, 1994, at 124.

[7]Continued spending on research in both public and private sectors reflects Americans' continued appetite for new medical technology. This appetite remains strong despite the turmoil within the health care industry over the last several years. *See* Peter J. Neumann & Eileen A Sandberg, *Trends in Health Care R & D and Technology Innovation*, HEALTH AFF., Nov.-Dec. 1998, at 111, 118; Mark R. Tonelli, Joshua O. Benditt, & Richard K. Albert, *Clinical Experimentation: Lessons from Lung Volume Reduction Surgery*, 110 CHEST 230, 235 (1996).

[8]In the case of high dose chemotherapy with autologous bone marrow rescue, "women were being told that the only chance they had in advanced breast cancer was bone marrow transplantation." Ed Susman, *Breast Cancer Doctors Call For More Bone Marrow Transplant Study*. BIOTECH. NEWSWATCH, June 7, 1999, at 12.

[9]It is rare for the marketplace to reject a new technology, regardless of its merit. Home uterine monitoring is an example of such a technology. It is commonly prescribed for women at high risk for premature deliveries, despite the fact that there is no evidence that it changes outcome. One expert obstetrician explained its popularity as "a mixture of companies that wish to sell their products and physicians who wish to impress their patients." *See* Terry, *supra* note 6 at 124. *See also* Tonelli, *supra* note 7, at 233 (noting that neither physicians nor patients appear willing or able to exercise discipline in utilization of unproven therapies and new technologies).

[10]*See* Michael Parrish, *It Could Happen to You*, HEALTH, May 15, 1996, at 114; David Leon Moore, *The $89 Million Question—Ethics Pinched the System, Lawyer Says*, USA TODAY, Jan 22, 1996, at 1D; *Patients are Opting for Unproven Care*, OMAHA WORLD-HERALD, Oct. 19, 1999, at 15A.

inability to discern experimental from established therapies, and/or an inability to distinguish between research protocol-costs and routine patient care costs which would have been incurred regardless of the patient's involvement in clinical research.[11] However, as health care costs inexorably increase[12] and the demand for evidence-based justification grows,[13] the difficult question of who should pay for care that is not yet of proven efficacy will become ever more pressing.

This article will explore the realm of clinical research and the question of who should finance such research. The first part will define the various types and levels of clinical research in terms of the regulatory controls and oversight applied to such research. Then the article will summarize how the costs of clinical research and experimental therapies have been covered in the past. Finally, the article will evaluate the risks and benefits derived by the various stakeholders and propose a financing rationale for therapies that places the burden of cost squarely on the stakeholders most likely to benefit.

CLINICAL RESEARCH: DEFINING THE SPECTRUM

Clinical research encompasses a wide range of medical interventions. The Institute of Medicine (IOM) recently defined clinical research as including:

- interventions to prevent, diagnose and treat disease;

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[11]*See* INSTITUTE OF MEDICINE, EXTENDING MEDICARE REIMBURSEMENT IN CLINICAL TRIALS 37 (2000) [hereinafter IOM Report].

[12]The United States health care system is the most expensive of all the world's systems, consuming 13.5 percent of the gross domestic product, exceeding a trillion dollars. Although the double-digit increases of the late 1900s have slowed, costs continue to rise faster than the rest of the economy. The government's share of the bill was 46 percent in 1997, compared to 40 percent in 1990. In addition, despite the cost of health care, approximately 16.1 percent (43.4 million persons) of the population has no health insurance. This percentage has continued to increase over the last several years. *See* John K Inglehart, *The American Health Care System*, 340 NEW. ENG. J. MED. 70, 72 (1999).

[13]*See* Tonnelli *supra* note 7, at 233-35 (discussing the importance of justifying new technologies with objective evidence before allowing them to be unleashed in the market); Steven H. Woolf, *The Need for Perspective in Evidenced-based Medicine*, 282 JAMA 2358, 2358 (1999) (favoring a national database compiling information about effective treatments for specific diseases.)

- drugs and devices; surgical, manipulative and other procedures; diagnostic laboratory tests, scans and examinations; dietary behavioral and psychological techniques;

- interventions associated with any illnesses or conditions (not limited to specific ones such as cancer, AIDS, and heart disease);

- new interventions, as well as "standard" interventions that have been used in a limited way (or extensively, but about which not enough reliable information is available);[14]

Research typically proceeds through phases of development, passing developmental milestones along the way.[15] In its infancy, clinical research may be merely a clinical innovation, acted upon in the exigency of a crisis or void, with no underlying study protocol or regulatory oversight.[16] If the innovation develops into legitimate research, it will be enveloped within a study regimen or protocol.[17] At the early stages, study protocols usually focus on the safety of the new drug, device or procedure using a single group of research subjects.[18] Such "single arm" trials generally are followed by more extensive studies that measure the experimental intervention against alternative therapies and/or involve a rudimentary comparison between experimental and "control" subject groups.[19] As the research further matures, the new intervention will be tested in a double-blind

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[14]*See* IOM Report, *supra* note 11, at 3.

[15]Research is described in federal regulations as "systematic investigation designed to develop or contribute to generalizable knowledge." *See* 45 C.F.R. § 46.102(e) (1999). Typically, research begins with animal studies, then continues with several phases of clinical trials using human subjects. *See* discussion *infra*, at p. 443.

[16]*See* IOM Report, *supra* note 11, at 3.

[17]*See* Dale L. Moore, *An IRB Member's Perspective on Access to Innovative Therapy*, 57 ALB. L. REV. 559, 562 (1994).

[18]*See* IOM Report, *supra* note 11, at 15-16; MICHAEL J. MALINOWSKI, BIOTECHNOLOGY: LAW BUSINESS & REGULATION 11-18-11-19 (1999).

[19]*See* IOM Report, *supra* note 11, at 15-16; MALINOWSKI, *supra* note 18, at 11-18-11-19.

randomized study, the so-called "gold-standard" of research.[20] Finally, the therapy will become a recognized standard of care.[21]

In some areas, such as the testing and development of new drugs, biologics, and medical devices, research can be easily categorized in terms of its stage of development because it is governed by a defined federal regulatory regimen.[22] However, in other areas, notably new procedures, there is no direct federal regulation, and oversight is limited to that administered by Institutional Review Boards (IRBs) or human subjects committees.[23] In addition, there is a category of "research" that is totally unregulated and largely unmonitored. This is the use of an innovative, unproven therapy, usually a procedure, to provide a "last best chance" for a patient who is dying or suffering with an incurable debilitating disease.[24] Such "last best chance" therapies may or may not be administered under a research protocol and may or

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[20]*See* IOM Report, *supra* note 11, at 17. *See generally* ROBERT J. LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH (2d ed. 1986); Samuel Hellman & Deborah Hellman, *Of Mice, But Not Men: Problems of the Randomized Clinical Trial*, 324 NEW ENG. J. MED. 1525, 1585 (1991) (discussing physician's ethical obligation to patients in a double-blind study); Jennifer Kulynuch, *Will FDA Relinquish the "Gold Standard" for New Drug Approval? Redefining "Substantial Evidence" in the FDA Modernization Act of 1997*, 54 FOOD AND DRUG L-4, 127 (1999) (discussing the onerous and costly nature of the requisite "gold standard").

[21]With drugs and devices, this stamp of approval is provided by the Food and Drug Administration. In the case of procedures, graduation to an accepted standard of care is murkier and is determined by peer reviewed medical journals, treatises, and occasionally, the courts.

[22]*See* discussion, *infra*, at p. 449 (discussing the role of Food and Drug Administration in the premarket approval of pharmaceutical drug, medical devices, and biologics).

[23]Any procedure that is being studied in a clinical trial funded through the federal government is required to comply with human subjects protections and must be approved by the IRB before the study is undertaken. However, use of an experimental procedure outside the context of a study protocol is not subject to such review and or monitoring. *See* discussion, *infra*, at p. 450.

[24]Procedures are susceptible to no legal requirements of safety and efficacy; nor do they have to be superior or equal to other alternatives in order to be used by practitioners. Indeed many procedures and medical interventions already well inculcated in health care have never been critically evaluated for evidence of safety or effectiveness. *See* IOM Report, *supra* note 11, at 4. In the case of high dose chemotherapy and bone marrow transplant for treatment of breast cancer, patients flocked to medical centers believing that the therapy was their only hope, despite the fact that its efficacy was unknown. The fact that such experimental procedures are unregulated and subject to no approval process, such as that applied to pharmaceuticals, allowed rapid market dispersion of an unproven, risky procedure. *See* Gina Kolata & Kurt Eichenwald, *Patients Skip Clinical Trials, Buy Treatments*, Portland Oregonian, Oct. 5, 1999, at A6.

may not adhere to established research principles and study design.[25] Indeed, the Institute of Medicine has pointedly excluded new interventions that might be adopted by practitioners treating patients outside of a research protocol from their definition of "clinical research."[26] Such interventions are considered to be in the earliest phase of innovation and not yet sufficiently developed to be recognized as "clinical research."[27]

Clinical Research in the Context of the Federal Regulatory Regimen

Much of clinical research is susceptible to federal regulation—either under the aegis of the Food and Drug Administration (FDA), the National Institutes of Health (NIH), or both.[28] The FDA provides an elaborate and detailed set of developmental milestones for new drugs, devices and biologics.[29] Indeed, many argue the process for research and development prescribed by the FDA is so onerous and complex that it thwarts dissemination of useful new therapies.[30]

The FDA approves and regulates drugs using one process mandated by the Food Drug and Cosmetics Act (FD&C Act),[31] medical devices by another, the Medical Devices Act of 1976 (MDA),[32] and biologics such as vaccines by a third—the Public Health Services

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[25]*See* Dale L. Moore, *Recurrent Issues in the Review of Medical Research on Human Subjects*, 1 ALB. L.J. SCI. & TECH. 1, 5 (1991).

[26]*See* IOM Report, *supra* note 11, at 3.

[27]*See id.*

[28]*See* Alan Kaplan, *50 Years of Drug Amendments Revisions, in Easy-to-Swallow Capsule Form*, 50 FOOD & DRUG L. J. 179, 179-81 (1995).

[29]*See id.*

[30]*See* Carolyn Lockhead, *A Deadly Over-Caution: FDA Assailed for Slow Testing of New Drugs*, S.F. CHRON., Oct. 26, 1992, at A1.

[31]21 U.S.C. §§ 301–393 (1994). The 1938 Food, Drug and Cosmetics Act (FD&C) superseded the Food and Drug Act of 1906, expanding the scope of product regulation dramatically. The 1938 Act imposed requirements upon drug manufacturers to file a new drug application before they marketed their products to the public. A series of amendments have modified and further expanded the scope of the 1938 Act, usually enacted in response to the expanding frontiers of science. These range from amendments added in 1941 to address a new biologic, insulin, to the Prescription Drug User and Generic Drug Enforcement Acts of 1992. Throughout its long history, the FDA has focused on regulating food and drug manufacturing to ensure safety and effectiveness. *See* Kaplan, *supra* note 28, at 182-85.

[32]*See* 21 U.S.C. § 360 (1994).

(PHS) Act.[33] Moreover, in some cases—typically with biological products—when the FDA exerts authority over the product, compliance with both the PHS provisions and FD&C provisions is required.[34]

Regulation of New Drugs and Pharmaceuticals

In the case of new drugs wending their way through the research pipeline, the FDA has rigorous safety and effectiveness standards guaranteed by a lengthy four-stage approval process.[35] This FDA regimen proceeds from an initial pre-clinical testing phase performed on animal subjects,[36] followed by an investigational new drug (IND) application requiring three phases of clinical research using human subjects.[37] These clinical trials must comply with human subjects protections and be approved by an IRB.[38] The most recent generic version of federal human subject protections is the "Common Rule," which has been adopted in a modified version by the FDA.[39]

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[33]*See* 42 U.S.C. § 262 (1994).

[34]For discussion of the relationship and interplay between the FD&C Act and the Public Health Service Act provisions, *see* Edward L. Korwek, *Human Biological Drug Regulation: Past, Present, and Beyond the Year 2000*, 50 FOOD & DRUG L. J. 123 (1995). Korwek notes that biologics products are simultaneously either biologics and drugs or biologics and devices under existing law; thus the major distinction is whether or not the contemplated product is a biologic; if so, it will be susceptible to two sets of regulatory requirements. *Id.* at 128. Adding another layer of complication is the fact that within the regulatory bureaucracy, separate regulatory centers deal with different FDA products. Drugs are evaluated by the Center for Drug Evaluation and Research (CDER) and biologics by the Center for Biologics Evaluation and Research (CBER). *See* Gary E. Gamerman, *Regulation of Biologics Manufacturing: Questioning the Premise*, 49 FOOD & DRUG L. J. 213, 213-16 (1994).

[35]*See* 21 U.S.C. § 355(b) (1994).

[36]*See id.*

[37]*See id.*

[38]In order to pass IRB muster, the proposed research must minimize the risks to subjects, use procedures that are consistent with sound research design, and whenever possible, be administered in the context of diagnosis and treatment purposes. *See* 45 C.F.R. § 46.111(a)(1) (1997). In addition, the risk to the subject should be reasonable in relation to the importance of the knowledge that is likely to result. *See* 45 C.F.R. § 46.111(a)(2) (1997). *See also* HHS Fact Sheet: *Protecting Research Subjects*, December 22, 1999, <http://waisgate.hhs.gov.> *See also* discussion on institutional review boards and human subjects protections, *infra*, at p. 450.

[39]*See* 56 Fed. Reg. 28012 (June 18, 1991). The Food and Drug Administration has adopted a modified version of the Common Rule, *see* 21 C.F.R. Parts 50 and 56. The Common Rule has been adopted by numerous other government agencies sponsoring research, notably the Department of Health and Human Services, *see* 45 C.F.R. Part 46 (1997).

In Phase I trials, the new drug is administered to a small group of healthy research subjects.[40] This early phase is designed to determine the chemical action of the drug, its safety and acceptable dosage range.[41] Phase II will involve a larger number of subjects who are usually patients being treated for the disorder that the drug is being developed to treat.[42] During this phase, researchers will elicit more discrete and detailed information about the effects of the proposed drug treatment; there is often some comparison between different study groups.[43] Finally, Phase III will compare the new drug with accepted alternatives or a placebo.[44] During Phase III, the standard is a randomized trial with experimental and control arms, usually involving a large number of subjects.[45] Phase III seeks to develop detailed information regarding both the safety and efficacy of the new drug as compared to existing accepted therapies.[46] The accumulated data is then submitted to the FDA in a new drug application (NDA) for evaluation, review and additional safety and effectiveness testing prior to FDA approval.[47] This process routinely takes a decade or more to complete and is extremely costly for the pharmaceutical manufacturer.[48] Post approval, Phase IV commences; it consists of

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[40]*See* MALINOWSKI, *supra* note 18, at 11-19.

[41]*See id.*; IOM Report, *supra* note 11, at 16.

[42]As such, the subjects are simultaneously patients. It is not infrequent for Phase I and II to be collapsed into a single phase. *See* 21 C.F.R. § 321. 21 (1994). *See also* MALINOWSKI, *supra* note 18, at 11-19.

[43]*See.* MALINOWSKI, *supra* note 18, at 11-19.

[44]*See id.*

[45]Thus, the patient persona of the subject will not necessarily receive a "treatment." This is cited as one of the primary reasons for difficulties in enrolling patients in Phase III trials. *See* GAO/HEHS 99-182, NIH Clinical Trials—Various Factors Affect Patient Participation, Sept. 30, 1999.

[46]*See* MALINOWSKI, *supra* note 18, at 11-19; IOM Report, *supra* note 11, at 16.

[47]*See* MALINOWSKI, *supra* note 18, at 11-19.

[48]The delays and time required in the current process are inextricably linked with cost. Industry experts report that taking the average drug from laboratory to market costs $400 million and requires 15 years. *See* John F. Niback, *Why Are Drug Development Programs Growing in Size and Cost? A View from the Industry,* 52 FOOD & DRUG L.J. 151, 181 (1997). Moreover, they estimate that 90 percent of the average cost is secondary to the regulatory delays. *See* Tanya Karwaki, *The FDA and the Biotechnology Industry: A Symbiotic Relationship,* 71 WASH. L. REV. 821, 828-29 (1996); Elizabeth M. Rutherford, *The FDA and "Privatization"—The Drug Approval Process,* 50 FOOD & DRUG L. J. 203, 212 (1995); Julie C. Relihan, *Expediting FDA Approval of AIDS Drugs: An International Approach,* 13 B.U. INT'L L. J. 229, 237 (1995).

post-marketing surveillance and monitoring of the drug's safety and efficacy.[49]

Regulation of Medical Devices

After a decade of somewhat bizarre efforts to classify certain devices as drugs in order to bring them under the FDA's more global regulatory umbrella,[50] the MDA replaced what had been after-the-fact regulation of already marketed devices with premarket review and approval.[51]

The MDA put in place a three-level classification system for medical devices and a regulatory regimen applicable to each of the classifications.[52] Class I devices are those for which safety and efficacy can be reasonably ensured by existing controls upon labeling and adherence to good manufacturing requirements.[53] Class II devices are those meeting Class I standards plus additional special control standards.[54] Class III devices are those that require a full pre-market clearance process, with presentation and review of clinical research documenting the safety and effectiveness of the new device.[55]

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[49]*See* Relihan, *supra* note 48, at 236-39 (1995); John P. Dillman, *Prescription Drug Approval and Terminal Diseases: Desperate Times Require Desperate Measures*, 44 VAND. L. REV. 925, 928 (1991).

[50]Without having statutory pre-market authority over medical devices and confronted with an increasing number of invasive technologies such as pacemakers, the FDA attempted to classify them as drugs. For example, suture material as well as implantable drug sensitivity disks were both deemed to be "drugs." *See* AMP, Inc. v. Gardner, 389 F.2d 825, 829 (2d Cir. 1968); United States v. An Article of Drug Bacto-Unidisk, 394 U.S. 784, 798 (1969).

[51]Although medical devices did come under the authority of the FDA to some degree in the 1938 Food, Drug and Cosmetic Act, the scope of this authority was limited to labeling requirements and removal from the market of adulterated or unsanitary devices. *See* Rodney R. Munsey, *Trends and Events in FDA Regulation of Medical Devices Over the Last Fifty Years*, 50 FOOD & DRUG L. J. 163, 167-68 (1995).

[52]*See* 21 U.S.C. § 360c(a) (1994).

[53]Class I devices must be manufactured by a FDA registered manufacturer, comply with Good Manufacturing Practice regulations, and be labeled in such a way that they are not misleading or false in any way. *See id. See also* Jay M. Zitter, *What is "Device" Within Meaning of Federal Food, Drug and Cosmetic Act* (21 U.S.C. § 321 (H), 129 A.L.R. Fed. 343 (1996).

[54]These special controls include performance standards, requirements for patient registries, and post-market surveillance of the device. *See* 21 U.S.C. § 360c(a)(1)(B) (1994).

[55]Class III devices are those whose reasonable safety and effectiveness can be assured only through compliance with a premarket clearance process. About 8 percent of regulated devices fall into class III. With respect to class III type devices that predated the MPA, the intent was to gradually retrospectively qualify them. *See* Munsey, *supra* note 51, at 168.

Obviously, because the medical device industry was fairly well developed by 1976—such devices as pacemakers, artificial heart valves and jaw implants were already common—the MDA had to distinguish these already marketed devices from those to come in the future.[56] After the implementation of the MDA, makers of devices purporting to meet Class I or Class II standards were required to submit to the FDA a 510(k) notification showing that the new product was substantially equivalent to an older Class I or Class II product.[57] Most of the medical devices of the late twentieth century are not Class I or Class II devices; instead they are high technology Class III devices, such as insulin pumps or implantable defibrillators.[58]

These new Class III type devices may pursue one of three courses to attain FDA authorization for marketing. They may apply for FDA clearance as a product which is "substantially equivalent" to another Class III product already marketed—the pre-market notification or the 510(k) route.[59] This requires the manufacturer to notify the FDA of the new product's substantial equivalence and present a modicum of data.[60] However, the 510(k) process does not require the rigorous *de novo* demonstration of safety and effectiveness that new devices not substantially equivalent to an already marketed Class III device must meet.[61] The 510(k) route was extensively utilized after enactment of the MDA in 1976.[62]

In the case of a novel, not-substantially equivalent product, the manufacturer must seek pre-marketing approval (PMA) from the

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[56]*See id.*

[57]*See id.*

[58]*See id.*

[59]*See id.* at 166.

[60]*See* Munsey, *supra* note 51, at 166.

[61]Because the full pre-market approval process is so onerous, the 510(k) route to market is preferred by manufacturers if the new device can be credibly proclaimed "substantially equivalent" to an earlier similar device. The 510(k) process requires only limited presentation of clinical trial evidence. The 510(k) method was particularly favored prior to 1990. Until 1990, the FDA allowed piggybacking of section 510(k)s—that is Product B could state it was substantially equivalent to pre-76 Product A; then Product C could get a 510(k) on the ground that it was substantially equivalent to Product B; and so on. Obviously with incremental changes, by the time you get out to Product Z, the differences between A and Z could be relatively dramatic. *See id.* at 169.

[62]*See id.*

FDA.[63] A PMA is essentially a product license from the FDA imposing precise conditions upon the manufacturing and labeling of the device, which serves to justify the FDA's approval of the device as safe and effective.[64] Like the NDA, the PMA process is rigorous, time consuming and expensive.[65] In the course of the PMA process, scientific evidence accumulated from controlled clinical trials must verify the safety and effectiveness of the device.[66] The medical device clinical trial process mimics that applied to drugs. However, the evidence that may be used to prove that the device is effective encompasses a broader scope of research than is generally allowed in validating pharmaceuticals.[67] Nevertheless, simple case reports, anecdotal evidence and mere opinion are not considered appropriate evidence.[68]

The third method by which a product may be used in the market is by an investigational device exemption.[69] This classification, instituted in 1980, requires FDA approval and compliance with human subjects protections when devices are used in clinical studies.[70]

The late 1980s brought increasing dissatisfaction with medical device regulation and the FDA and its Center for Devices and Radiological Health (CDRH).[71] This stimulated legislation which eventually was enacted as the Safe Medical Devices Act of 1990 (SMDA).[72] The SMDA was designed to increase the FDA's post-market tracking of devices in all categories, including those marketed prior to 1976.[73] It also tightened the requirements for 510(k)

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[63]*See id.*

[64]*See id.*

[65]The process includes the participation of numerous outside experts and careful review of the scientific data and studies showing the safety and efficacy of the device. *See* Munsey, *supra* note 51, at 166.

[66]*See* 21 C.F.R § 860.7(c)(2) (1997). *See* 21 C.F.R § 814.20(b)(3)(B) (1997).

[67]For example, evidence used in qualifying a device may come from controlled scientific trials, but may also come from other "valid scientific evidence" that speaks to the effectiveness of the device. *See* Munsey, *supra* note 51, at 166.

[68]*See* 21 C.F.R. § 860.7(c)(2) (1997); 21 C.F.R. § 814.20 (b)(3)(B)(1997).

[69]*See* Munsey, *supra* note 51, at 166-69.

[70]*See id.*

[71]This criticism focused on PMA delays, lax reporting of adverse events, and slowness in developing standards for devices. *See id.* at 171.

[72]*See* 21 U.S.C. § 360i(b) (1994).

[73]*See* Munsey, *supra* note 51, at 172.

notification, making this route to market less feasible, thus forcing "new" devices to seek a full PMA.[74]

As a result of the MDA and subsequent SMDA, the regulatory regimen for medical devices is increasingly similar to that for drugs.[75] Manufacturers are held to strict safety and manufacturing standards.[76] In the case of novel, not "substantially equivalent" devices, rigorous clinical trials and presentation of evidence obtained from them must be reviewed and evaluated by the FDA before the device may be marketed.[77]

Regulation of Biologics and Vaccines

Yet another set of medical products that is regulated by the FDA is biologics.[78] The statutory provisions governing biologics like vaccines actually predate the 1906 Food and Drug Act.[79] Congress took action to regulate such biologics in 1902 after a number of highly publicized deaths resulted from contaminated diphtheria vaccine.[80] Despite the early legislative action and statutory authority, regulation of biologics was largely unenforced until the 1950s.[81] Today, however, biologics regulation is a complex maze of requirements and licensure designed to assure safe and unadulterated biologics products.[82]

The Center for Biologics Evaluation and Research (CBER) reviews the safety and efficacy of biologics, monitors clinical testing of

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[74]The SMDA essentially closed the sequential "piggy-backing" loophole that evolved after the passage of the Medical Devices Act. *See id.*

[75]*See* J. Matthew Buchanan, *Medical Device Patent Rights in the Age of FDA Modernization: The Potential Effect of Regulatory Streamlining on the Right to Exclude*, 30 U. TOL. L. REV. 305, 310 (1999).

[76]*See id.* at 305.

[77]*See id.*

[78]Biologics include: vaccines, viruses, therapeutic serums, toxins, antitoxins, blood, blood component or derivatives, and allergenic products. *See* 42 U.S.C. § 262 (1994). Excluded are antibiotics and hormones (usually regulated as drugs). *See* 21 U.S.C. §§ 355-357 (1994).

[79]*See* Gamerman, *supra* note 34, at 215.

[80]*See* Philip D. Noguchi, *From Jim to Gene and Beyond: An Odyssey of Biologics Regulation*, 51 FOOD & DRUG L.J. 367, 368 (1996).

[81]*See* Gamerman, *supra* note 34, at 218.

[82]This includes regulations defining what constitutes "manufacturing," which activities require an establishment license, compliance with one or two forms of manufacturing arrangements, and strong FDA preference for integrated manufacturing. *See* Gamerman, *supra* note 34, at 221.

biological products, establishes product standards, conducts some specialized research, and administers the licensing of blood banks and vaccine manufacturers.[83] Ultimately biologics research culminates in a biologics license application (BLA), the biologics analog of the NDA for drugs.[84] This BLA process represents a streamlining of the biologics approval process resulting from the FDA Modernization Act of 1997.[85] Nevertheless, like drug and device regulation, biologics regulation requires evidence of safety and efficacy generated through reproducible clinical trials.[86]

In sum, the FDA has detailed an extraordinarily risk-averse regulatory scheme for pharmaceutical drugs, medical devices and biologics.[87] These products cannot be marketed by manufacturers without FDA approval.[88] Regardless of whether the new therapy is susceptible to regulation as a drug, a device or biologic, the FDA prescribes discrete stages of research prior to FDA approval and authorization for marketing.[89] Each stage is replete with requirements for up-front evaluation of study protocols, oversight by IRBs, analysis and peer review of research results, and careful determination of safety and efficacy standards.[90] Thus, the developmental steps in bringing a new drug, device or biologic from research to market are easily defined and documented. Unfortunately, there is no parallel process for new treatment procedures.

Procedures: The Unregulated Frontier in Clinical Research

In contrast to drugs, devices and biologics, procedures are not subject to dedicated federal regulation.[91] Nevertheless, some clinical research

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[83] *See* MALINOWSKI, *supra* note 18, at 11-15

[84] *See id.*

[85] *See* FDA Modernization Act (FDAMA) Pub. L. No. 105-115, 111 Stat 2296 Sec. 210 (1997). Prior to the BLA, biologics products were required to obtain both a product license application (PLA) and an establishment license application (ELA). *See* MALINOWSKI, *supra* note 18, at 11-16.

[86] *See* MALINOWSKI, *supra* note 18, at 11-21

[87] *See id.*

[88] *See id.*

[89] *See id.*

[90] *See id.*

[91] *See* IOM Report, *supra* note 11, at 4. Many scholars argue that the lax standard applied to procedures versus that applied to drugs is not only inconsistent and detrimental to scientific evaluation, but is unethical. *See* Tonelli, *supra* note 7, at 230. Similarly in the case

involving procedures is funded with government grant money, usually through the NIH.[92] Because of this federal funding, the research is required to comply with federal regulations protecting human subjects and oversight by an IRB.[93]

Institutional Review Boards: Safeguarding Research Using Human Subjects

IRBs or Human Subjects Committees are charged with protecting human subjects who are enrolled in federally funded or sponsored research.[94] The IRB is composed of not only researchers, but several other classes of members designated by federal regulation.[95] The constitution of the committee is designed to provide a global and unbiased review of the research.[96]

The IRB's primary focus is the safeguarding of human subjects.[97] It will evaluate the proposed research project with respect to methods of subject recruitment and evaluate the risks and benefits of the research for the subject.[98] The IRB will review and verify that the

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of the HDC/ASCR treatment for breast cancer, oncologists promoted the unproven treatment with complete impunity. Indeed, even the American Society of Clinical Oncology was emphatically touting the therapy as superior as early as 1992. *See* Napoli, *supra* note 148.

[92]Drug and device research may also be subject to NIH requirements if the research is federally funded rather than funded by the private sector. The NIH, its companion institutes, and various bureaus address a broad scope of research, including cancer (National Cancer Institute (NCI)), heart disease (National Heart, Lung and Blood Institute), and mental health and substance abuse (Alcohol, Drug Abuse and Mental Health Administration (ADAMHA)). *See* INSTITUTE OF MEDICINE, FUNDING HEALTH SCIENCES RESEARCH 37-38 (1996) [hereinafter Funding Health Sciences Research]. In addition, numerous other federal entities sponsor medical research and clinical trials, including the National Science Foundation (NSF), Centers for Disease Control (CDC), the Department of Veteran's Affairs, National Aeronautics and Space Administration (NASA), and the Department of Defense. *See id.* at 38-47.

[93]*See* 45 C.F.R. § 46 (1997); JEREMY SUGARMAN, ANNA C. MASTROIANNI, JEFFREY P, KAHN, ETHICS OF RESEARCH WITH HUMAN SUBJECTS: SELECTED POLICIES AND PROCEDURES 33 (1998); Mary Terrell White, *Guidelines for IRB Review of International Collaborative Medical Research: A Proposal*, 27 J. L. MED. & ETHICS 87, 87 (1999).

[94]*See* 45 C.F.R. § 46.101 (1997).

[95]*See* 45 C.F.R. § 46.107 (1997).

[96]The regulations take great care to ensure that the committee will be balanced in terms of gender, profession, and affiliation. IRB members are foreclosed from participating in review of any project or study in which they have a conflicting interest. *See* 45 C.F.R. §§ 46.107 (b)-(e) (1997).

[97]*See* 45 C.F.R. § 46.101(a) (1997).

[98]*See* 45 C.F.R. § 46.111(a)(3) (1997).

consent document is fully informative, unambiguous, and comprehensible to the subject.[99] IRBs seek to minimize risks to subjects, guard privacy and confidentiality, ensure good study design, and foster research that maximizes benefit to the individual subject while advancing the frontiers of research.[100]

Federal law requires that all research that is funded or sponsored by federal dollars must be approved by the IRB before it is undertaken.[101] In addition, most universities and medical research centers require that all research, regardless of funding source, comply with federal human subjects requirements.[102]

The federal regulations protecting human subjects thus capture another category of research—new procedures that are being researched with federal funding or in an institution that is subject to the federal human subjects regulations.[103] This allows for such research to be designated as clinical research under an evaluated and IRB-authorized study protocol.[104] Such clinical trials of procedures will seek to verify that the new procedure is safe and effective.[105] Also, the clinical trials will attempt to show that the new procedure is better than, or at least equivalent to, the established procedures used in treatment of the malady.[106] This legitimate research will be informally classed as Phase I, Phase II, or Phase III to be consistent with the vernacular applied to pharmaceutical research.[107]

However, IRB review and monitoring does not apply to experimental medical innovations that are not part of an established protocol or merely defined as "research" by the provider.[108] These new procedures range from the well-accepted not-so-new, but untested

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[99]*See* 45 C.F.R. § 46.116 (1997).

[100]*See* 45 C.F.R. § 46.111(a) (1997).

[101]*See* 45 C.F.R. § 46.103(b) (1997).

[102]*See* Moore, *supra* note 17, at 560. Indeed, most large universities and centers have obtained a multiple project assurance (MPA) that governs both federally and non-federally funded research. *See* SUGARMAN, *supra* note 93, at 33.

[103]*See* 45 C.F.R. § 46.101(a) (1999). These clinical trials are subject to IRB funding by virtue of their federal funding or sponsorship, rather than on the basis of their need for federal approval prior to being authorized for marketing. *See* IOM Report, *supra* note 11, at 22-23.

[104]*See* IOM Report, *supra* note 11, at 15.

[105]*See id.* at 16.

[106]*See id.* at 22-23.

[107]*See id.* at 17.

[108]*See* Tonelli, *supra* note 7, at 230.

innovations[109] to new "last best hope" procedures directed at a dying patient who has failed to respond to accepted, conventional treatment.[110] The latter captures headlines and sparks emotion, and has generated much of the controversy with respect to funding of "research."[111]

Experimental Procedures and Treatments: Innovation as a Last Resort

Despite our technologic achievements, medicine and science continues to be bedeviled by stubborn challenges like AIDS and common cancers that are resistant to all our weapons.[112] Often the victims of these stubborn killers are young, sick, desperate and out of options. Innovative treatments, even those of unproven value, are a powerful lure for these patients, their families, and their health care providers.[113] Often, these treatments are not part of a legitimate research trial[114] and do not qualify for funding as such, nor are they established treatments eligible for coverage by third party payers.[115]

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[109]*See* Eddie Gibb, *Just Chew It*, SUNDAY HERALD, Jan. 9, 2000, at 16 (discussing use of St. John's Wort for depression); Sheila Anne Feeney, *The Agony of Acne*, THE MILWAUKEE JOURNAL SENTINEL, March 6, 2000, at G1 (discussing the well-advertised use a of specific birth control pill to improve acne).

[110]There are numerous accounts of such cases in the lay press. In one reported case, the patient's husband described his wife's long and torturous death from breast cancer, during which she chose twice to undergo high dose chemotherapy and autologous bone marrow transplant, knowing that it was unproven and unlikely to work. Her husband, a physician, was incredulous when the doctors were willing to perform the second transplant. *See* Judy Foreman, *Marrow Transplants Falling Short of a Miracle—Efficacy Against Breast Cancer Unclear*, BOSTON GLOBE, Apr. 3, 1999, at B1.

[111]*See id.*

[112]AIDS and Breast Cancer, both highly visible and well-publicized killers, are the two top recipients of federal grant money. Awarded $1.4 billion and $381.9 million respectively in fiscal year 1996, they receive a share of research funds that is out of proportion with disability-adjusted life years that they take. *See* Katharine Webster, *AIDS, Breast Cancer Research Get Most Federal Funding*, PATRIOT LEDGER, June 18, 1999, at 11.

[113]*See* Foreman, *supra* note 110, at B1.

[114]Notwithstanding the fact that the treatment is not part of a legitimate trial and not compliant with human subjects protections required of legitimate research, entrepreneurial providers often do describe their services as a "clinical trials program." This marketing tool has been to used to the advantage of Response Oncology, a for-profit chain offering high dose chemotherapy and stem cell rescue to cancer patients. Despite the label, the program administered the procedure to all patients without any guise of a scientific protocol or study in place. *See* Kolata & Eichenwald, *supra* note 24, at A6.

[115]*See id.*

One such common cancer that has proven recalcitrant to treatment is breast cancer. Afflicting one in every eight women,[116] the incidence of breast cancer has remained relatively constant since the turn of the last century.[117] Although it increases in incidence with age, many of its victims are not old but are in the prime of their lives.[118] Worse still, many of these young breast cancer patients have particularly virulent forms of the disease and a dismal prognosis.[119]

In the 1980s and 1990s, the search for better breast cancer treatments led to increased use of chemotherapy, both in terms of drugs utilized and dosages administered.[120] The limiting factor was believed to be the deadly effect of higher chemotherapy doses on the patient's bone marrow.[121] The drugs would virtually decimate the marrow, leaving the patient with numerous toxic side effects.[122] Researchers sought to curtail these severely adverse side effects by re-infusing harvested bone marrow to rescue the patient after high dose chemotherapy.[123] These autologous bone marrow transplants (ABMT),[124] and the subsequent improved procedure, autologous stem cell rescue (ASCR),[125] were seized upon by physicians and patients alike as a new, more aggressive, treatment for advanced breast cancer.[126]

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[116]This equates to approximately 44,000 deaths from the disease every year. *See* Sandra G. Boodman, *Breast Cancer Roulette*, WASH. POST, Apr. 27 1999, at Z12.

[117]*See* Bernard Fisher, et al., *Neoplasms of the Breast in* CANCER MEDICINE 2349, 2380 (James F. Holland et al., eds., Williams & Wilkins, 1998).

[118]*See id.*

[119]*See id.*

[120]*See* J. Zujewski, A. Nelson & J. Abrams, *Much Ado About Not Enough Data: High Dose Chemotherapy with Autologous Stem Cell Rescue for Breast Cancer*, 90 J. NAT'L CANCER INSTITUTE 200, 200-08 (1998) [hereinafter Zujewski.].

[121]*See id.*

[122]*See id.*

[123]*See* American Society of Clinical Oncology, *The Role of High Dose Chemotherapy and Bone Marrow Transplant or Peripheral Stem-Cell Support in the Treatment of Breast Cancer: Background and Preliminary Results of Five Studies Presented at the ASCO's Annual Meeting*, May 15-18, in Atlanta, GA, <http://www.asco.org> [hereinafter ASCO].

[124]*See id.*

[125]In the autologous bone marrow procedure, stems cells are withdrawn from the marrow, frozen and then later reinfused into the patient. In the peripheral stem cell procedure, the stem cells are forced out of the marrow with medication into the peripheral blood stream where they can be retrieved by a simple blood draw. The later improvement spares the patient an invasive bone marrow aspiration for initial harvesting of marrow cells. *See id.*

Despite fervent belief in these therapies, there was little research demonstrating the safety and efficacy of the procedures.[127] Indeed, the tremendous demand for the procedure resulted in its rapid adoption by a market of young, desperate breast cancer patients who saw the high dose chemotherapy (HDC) followed by either autologous bone marrow transplant (HDC/ABMT) or high dose chemotherapy followed by either autologous stem cell rescue (HDC/ASCR) as a last chance for a cure.[128]

This final chance had a high price tag, both in terms of morbidity and mortality, as well as dollars. The procedure was and is expensive, costing at least $100,000 and often twice that.[129] The toxicity of the drugs results in life-threatening infections, bleeding disorders, organ dysfunction, severe skin rashes and allergic reactions, severe nausea and gastrointestinal problems, and numerous other adverse side effects.[130] Death as a result of the therapy occurred in up to 20 percent of cases, although experience with the procedure has dropped the mortality rate significantly.[131]

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[126]*See* Kolata & Eichenwald, *supra* note 24, at A6. *See also* Sandra G. Boodman, *New Breast Cancer Studies Blunt Hope—Bone Marrow Transplant No Wonder Cure*, New Orleans Times-Picayune, May 2, 1999, at A24 ("Four of five studies involving 2,000 women found that for those newly diagnosed with aggressive cancers or for those whose cancers have recurred and spread far outside the breast, transplants appear to be no better than conventional chemotherapy in prolonging life").

[127]*See* ASCO, *supra* note 123. *See also* Scott Gottlieb, *Bone Marrow Transplants Do Not Help in Breast Cancer*, 170 WEST. J. MED. 376, 380 (1999) ("Preliminary results released early from 4 ongoing clinical studies of breast cancer treatments indicate that high-dose chemotherapy followed by bone marrow transplantation may not significantly improve survival, although positive results from a fifth trial, also released early, seem to suggest otherwise").

[128]Approximately 30,000 women are believed to have received high dose chemotherapy and autologous/stem cell rescue, although only a small fraction of them were enrolled in legitimate trials. *See Patients Are Opting for Unproven Care*, OMAHA WORLD-HERALD, Oct. 10, 1999, at 15A. *See also* Kolata & Eichenwald, *supra* note 24, at A6 (calling experimental treatments a "growing business").

[129]*See* Bruce E. Hillner, Thomas J. Smith & Christopher Desch, *Efficacy and Cost Effectiveness of Autologous Bone Marrow Transplantation in Metastatic Breast Cancer: Estimates Using Decision Analysis While Awaiting Clinical Trial Results*, 267 JAMA 2055, 2055 (1992).

[130]*See* Zujewski, *supra* note 120, at 200-08.

Market adoption was not hindered by lack of FDA approval because, as a procedure, HDC/ASCR was not susceptible to any regulatory approval.[132] IRBs reviewed the treatment protocols for adequate human subjects protections in only a small fraction of cases.[133] Of the 12,000-30,000 women in the United States who underwent HDC/ASCR, only about one thousand of them are believed to have been enrolled in a legitimate clinical trial.[134]

Because of the uncontrolled access to the procedure, outcome and reliable research data were slow to emerge.[135] Indeed, only a few randomized controlled clinical trials comparing HDC/ASCR with conventional chemotherapy have been undertaken.[136] In retrospect, the fervent adoption of the HDC/ASCR procedure for breast cancer treatment actually undermined efforts to accrue reliable data, thus slowing the determination of its safety and efficacy.[137]

It was not until mid-1999 that preliminary results of a body of research were released by the National Cancer Institute (NCI) and unveiled at a meeting of the prestigious American Society of Clinical Oncology (ASCO).[138] These results were drawn from five randomized

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[131]Mortality rates during the early years of doing the procedures were as high as 20 percent. Current mortality from the therapy is believed to be about 5 percent so long as the therapy is provided in a center experienced in doing the procedure. However, in the largest randomized trial to date mortality for high dose chemotherapy was 7.9 percent. *See* ASCO, *supra* note 123.

[132]*See id.*

[133]*See* GAO/HEHS 96-83 *supra* note 2; Zujewski, *supra* note 120, at 200-08; Sandra G. Boodman, *Breast Cancer Roulette*, WASH. POST. Apr. 27, 1999, at Z12.

[134]Because of the uncontrolled market adoption, it is impossible to know how many women have received the procedure. *See Patients Are Opting for Unproven Care, Not Scientific Study*, OMAHA WORLD-HERALD, Oct. 10, 1999, at 15A.

[135]*See* GAO/HEHS 96-83, *supra* note 2; Zujewski, *supra* note 120, at 200-08; Boodman, *supra* note 116, at Z12.

[136]*See* ASCO, *supra* note 123.

[137]Several advocates and researchers have opined that had bone marrow transplant been provided in clinical trials rather than on the basis of ad hoc demand, researchers would have had answers to questions of safety and efficacy years ago. *See* Boodman, *supra* note 133, at Z12.

[138]*See* ASCO, *supra* note 123; the results were initially displayed on the Web due to pressure exerted by patients and doctors, and release was preceded by a meeting at the National Cancer Institute focusing on how to release the disappointing data given the public investment in the procedures. *See* Judy Foreman, *When Hopes Run Ahead of Facts*, MPLS. STAR-TRIBUNE, Apr. 4, 1999, at 3E; Michael Waldholz, *Breast Cancer Studies Question Bone Transplants*, WALL. ST. J., Apr. 16, 1999, at B7.

clinical trials, two of which involved subjects with advanced metastatic breast cancer[139] and three involving subjects with breast cancer that had spread to multiple lymph nodes.[140]

Four studies, including the largest randomized trial, found no significant difference between HDC/ASCR and conventional chemotherapy.[141] In one study, 7.4 percent of patients in the HDC/ASCR arm of the study died, as compared to no deaths in the conventional chemotherapy "control" group.[142] This study was conducted at several large academic medical centers where researchers were highly skilled in the procedure, and the study's principal investigator was one of the most vociferous proponents of HDC/ASCR.[143]

One of the five studies showed fewer cancer relapses and lower mortality in the HDC/ASCR arm of the study.[144] This study, performed in South Africa with a relatively small sample of subjects, was expected to bolster the belief that the HDC/ASCR procedure was a worthwhile treatment.[145] However, some argued that the two arms of the study were unbalanced in terms of prognostic factors, and the non-HDC "control" group did not receive conventional chemotherapeutic regimens.[146] These criticisms prompted a review and verification of the results after presentation of the paper.[147]

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[139]One of these studies was done at the University of Pennsylvania with 553 initial subjects, but only 199 patients finished the trial. The remaining 354 either chose not to be randomized or were found ineligible on the basis of their disease status. The other study was done in Paris with only 61 subjects. *See* ASCO, *supra* note 123.

[140]One of the high-risk primary breast cancer studies was done in the United States; 783 women participated in the study. Another study was done in Sweden with 525 subjects. The third was done in South Africa and involved only 154 subjects. *See* ASCO, *supra* note 123.

[141]*See id.*

[142]*See id.* (Abstract of Study #2).

[143]William Peters, principal investigator of that trial and president of the Barbara Ann Karmanos Cancer Institute in Detroit, has been a leading advocate of insurance coverage of bone-marrow transplants for patients in clinical trials and a pioneer in developing the treatment. *See* Nancy Ann Jeffrey & Ron Winslow, *New Clash Seen Over Treatment Of Breast Cancer*, WALL ST. J., Mar. 8, 1999 at B1.

[144]*See* ASCO, *supra* note 123 (Abstract of Study #4, a study done at the University of Witwatersrand Medical School, Johannesburg, South Africa, by Dr. W.R. Bezwoda.).

[145]*See* Michael Waldholz, *Doctor Admits Falsifying Data*, N.Y. TIMES, Feb. 5, 2000, at B2.

Nine months later, review and further inquiry revealed that the South African investigator had falsified his data.[148] The study was discredited, and the researcher resigned from his university admitting that he had "committed a serious breach of scientific honesty and integrity."[149]

The disappointing results of this once highly touted procedure have resulted in reflection and reassessment by providers and patient advocates alike.[150] One researcher stated that there is not enough evidence to say that high dose therapy is more effective than the standard therapy; therefore, the researcher does not recommend its routine use.[151] Although some patient advocates remain firmly in favor of this treatment,[152] others argue that it is time to recognize that HDC/ASCR "have no benefit" in the treatment of breast cancer and its popularity is a "triumph of hope over experience."[153] Even more

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[145]*See* Philip R. Rowlings, *Factors Correlated with Progression-Free Survival After High Dose Chemotherapy and Hematopoietic Stem Cell Transplantation for Metastatic Breast Cancer*, 282 JAMA 1335, 1335 (1999).

[147]*See id.*

[148]*See* Denise Grady, *Breast Cancer Researcher Admits Falsifying Data*, N.Y. TIMES, Feb. 5, 2000, at A9; Michael Waldholz, *Doctor Admits Faking Data on Cancer Therapy*, WALL ST. J., Feb. 5, 2000 at B2; Lauran Neergaard, *Scientist Falsified Data Supporting Cancer Regimen*, SEATTLE TIMES, Feb. 5, 2000, at A2; Mary Ann Napoli, *Oncologists Guilty of Giving Unproven Treatment—Case of Fraud Instructive for People with Cancer*, HEALTH FACTS, Apr. 1, 2000, *available at* 2000 WL 7525107

[149]*See* Grady, *supra* note 148, at A9.

[150]"Doctors and patients are rethinking the use of transplants," reported one researcher. Another noted "[t]here has been a lot of hype about the benefits of bone marrow transplants without any clear evidence,...[t]hese data will remind women that they have a choice." PEORIA J. STAR, May 18, 1999, at A10.

[151]*See* Lorilyn Rackl, *Study Raises Doubts of Bone Marrow Transplant for Breast Cancer Patients*, CHICAGO DAILY HERALD, April 19, 1999, at 3 (quoting Dr. Richard Shilkey, Director of the Cancer Research Center, University of Chicago).

[152]One patient advocacy group, the Susan G. Komen Breast Cancer Foundation stated:

> [T]he results of these studies in no way suggest that this matter is settled. The length of the follow-up in these studies is still relatively short, and additional data analyses need to be completed. Pending longer follow-up and subgroup analyses, the Komen Foundation will continue to encourage breast cancer patients considering this treatment to consult with their oncologist to review the risks and the benefits and to seek an unbiased second opinion when warranted.

TRANSPLANT NEWS, Apr. 30, 1999.

[153]*See* Boodman, *supra* note 115, at Z12 (comments of Fran Visco, President of the

sobering is the belief by researchers that "mutual self-deception"[154] and "emotions and biases interfered" with timely completion of the desperately needed studies.[155] Certainly the recent revelations involving the South African study have further validated that view.

FINANCING OF CLINICAL RESEARCH: WHO DOES PAY AND WHEN?

There is a widespread concern that lack of financing chills participation in clinical trials.[156] However, there is little empirical evidence supporting this belief.[157] A recent report issued by the Institute of Medicine (IOM) found that this belief is based more on perception than reality.[158] Nevertheless, the cost of clinical research has become an increasingly contentious question in the United States. The costs can be roughly divided into research protocol-related costs and routine patient costs sustained by the subject during the course of the clinical trial.

Although the federal government was once viewed as the preeminent funding source, researchers are currently obtaining private funding (or significant supplementation of federal dollars) with increasing frequency.[159]

Federal Funding: Sustaining the Publicly Funded Research Enterprise

Traditionally, the research making the United States a leader in medical technology and innovation was funded by federal grant money awarded

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National Breast Cancer Coalition and member of the Institute of Medicine's National Cancer Policy Board).

[154]*See* Foreman, *supra* note 138, at 3E (quoting medical ethicist George Annas.)

[155]*See* Meredith Goad, *Studies May Aid In Breast Cancer Fight, Data About Bone Marrow Transplants Could Help Patients, Doctors and Hospitals Decide on Treatment*, PORTLAND PRESS HERALD, Apr. 14, 1999, at B1 (quoting Dr. John K Erban, Chief of Oncology, New England Medical Center).

[156]*See* IOM Report, *supra* note 11, at 53.

[157]*See id.* at 37.

[158]*See id.* at 2, 6,

[159]*See* David Blumenthal, Nancyanne Causino, Eric Campbell, & Karen Seashore Lewis, *Relationships Between Academic Institutions and Industry in the Life Sciences*, 334 NEW ENG. J. MED. 251, 368 (1996).

by the NIH.[160] Indeed, we are only now emerging from what has been described as the "golden era" of the NIH.[161] This golden era, which commenced following World War II, converted the NIH from a small group of laboratories in Bethesda, Maryland to a massive research enterprise that stretches far beyond the Bethesda campus.[162] The various national institutes fund and apportion money to research centers all over the nation.[163] In 1995, 35.8 billion dollars were dedicated to research, comprising 3.5 percent of health expenditures.[164] This percentage has risen steadily over the last forty years.[165]

Funding is granted by the NIH after careful peer review of the proposed study.[166] Peer reviewers critically evaluate the submissions in terms of merit and flaws in research methodology.[167] If the project is chosen for funding, the money is dispensed in accordance with the submitted, agreed upon budget.[168] This budget will include provisions for the costs of the study, salary for the researchers, and subject costs.[169] Such federally funded studies must comply with the federal regulations protecting human subjects, independent of whether they

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[160]This tradition is relatively short-lived. Prior to World War II, health research was financed primarily by industry, academic institutions, and private philanthropy. However, in the aftermath of the War, the federal government poured money and resources into medical research. *See* FUNDING HEALTH SCIENCES RESEARCH, *supra* note 92, at 32-34; Harold Varmus, *Biomedical Research Enters the Steady State*, 333 NEW ENG. J. MED. 745, 812 (1995); GAO-HEHS 99-182, NIH Clinical Trials—Various Factors Affect Patient Participation., Sept. 30, 1999.

[161]*See* Varmus, *supra* note 160, at 812.

[162]*See id.*

[163]Approximately two-thirds of federally sponsored research is conducted in academic institutions, whereas only about a quarter is conducted in government-owned laboratories, such as those on the Bethesda campus. This decentralization is viewed as one of the key reasons for America's research eminence. *See* Funding Health Sciences Research, *supra* note 92, at 35-36; *see also* Varmus, *supra* note 160, at 812.

[164]*See* Inglehart, *supra* note 12, at 72.

[165]For example, in 1960 the federal government spent $700 million on research as compared to the $18 billion it spent in 1997. *See* Inglehart, *supra* note 12, at 73. In percentage terms, research consumed 3.5 percent of health care expenditures in 1995, as compared to 3.2 percent in 1986. *See id.* at 74; Neuman & Sandberg, *supra* note 7, at 112.

[165]*See* Funding Health Sciences Research, *supra* note 92, at 93.

[167]This competitive process typically has two sequential levels of review. First, there is a review by a select group of scientist peers in "study sections." Second, there is review by the advisory committees of the NIH institute. *See id.*

[168]*See id.*

[169]*See id.* at 99-100.

would have had to comply by virtue of being a FDA regulated product.[170] Research involving procedures, however, may not involve a product governed by the FDA process.

In some cases, federally funded research will be carried out in General Clinical Research Centers (GCRC).[171] These centers are comprised of NIH-funded hospital beds reserved for NIH-funded research.[172] Studies involving GCRC beds use rigorous guidelines to distinguish between routine care costs and those associated with the research study.[173] Routine, non-research related costs are billed to the subject patient's third-party payer and research protocol-related costs are borne by the research grant.[174] Although the GCRC model represents the ideal research setting, most research will not be carried out in this manner.

A typical medical center, even an academic teaching facility, will lack the resources to adequately differentiate between costs applicable to research procedures versus other procedures.[175] In most cases, third-party payers will be billed for all costs and will have the burden of reviewing claims to determine which services performed were routine and not research protocol-related, and thus eligible for coverage.

Private Sector Financing

Despite the generous federal funding that researchers have enjoyed for the past several decades, the trend is toward a greater percentage of research being funded by the private sector.[176] The proportion of research that is paid for by pharmaceutical, medical device and other private sector industry has steadily increased. In 1986, the private sector funded 42 percent of health care research and development. By 1995, the private sector's allocation of research dollars had risen to 52 percent.[177] This equated to a three-fold increase in absolute dollars, *i.e.*

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[170]*See id.*

[171]*See* Funding Health Sciences Research, *supra* note 92, at 99-100.

[172]The GCRC Program usually supports defined areas within academic medical centers. Among the special areas of focus are AIDS and other infectious threats. *See id.* at 107.

[173]*See* IOM Report, *supra* note 11, at 41

[174]*See id.* at 41.

[175]*See id.* at 41.

[176]*See* Neumann & Sandberg, *supra* note 7, at 111.

[177]*See id.*

from approximately $6 billion to $19 billion.[178] Thus, although the federal funding of research has incrementally increased over time, the private funding has increased exponentially.

Private funding of research is heavily skewed to drugs, devices and biologics, rather than to medical procedures.[179] These therapies are researched and developed by large, often international manufacturing firms.[180] Although the early phases of the research is performed within the pharmaceutical or device firms laboratories, once the new technology is ready for testing on human subjects, the locus of the research is moved to a clinical setting, and the clinical trial commences in one or more academic medical centers.[181]

Many of the private dollars financing clinical research are filtered to research centers by Contract Research Organizations (CROs).[182] This is especially true in the context of the large Phase III multi-center clinical trials.[183] CROs contract with academic medical centers, arrange the multi-center trial, and handle the administrative aspects of the trial.[184] In essence, CROs move dollars from the wealthy pharmaceutical and medical device industry to academic clinical research centers.[185] They will pay the academic research centers and researchers for conducting the trial, cover the costs of recruiting and caring for the subjects, and supply the drug or device that is being researched.[186] They will monitor the trial to be certain that the research has been approved by the IRB and other necessary committees.[187]

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[178]*See id.* at 112.

[179]*See id.*

[180]*See id.*

[181]Indeed, the trend is to greater outsourcing of research. *See* Andrew E. Kantra & Andrea V. Nassan, *Contract Research Organizations: Careful CRO Selection as a Tool to Avoid Potential Risks*, 1118 PLI/Corp 301, 305 (1999).

[182]*See id.* at 306. Ninety percent of companies conducting life sciences research had relationships with academic institutions in 1994. About half of the companies interacting with academic centers support clinical trials. *See* Blumenthal, *supra* note 159, at 368.

[183]*See* Kantra & Nasson, *supra* note 181, at 307-08.

[184]*See id.* at 306-07.

[185]*See Role of Contract Research Organizations to Increase in Pharmaceutical Industry*, MARKETLETTER, Mar. 29, 1999, at 1.

[186]*See id.*

Private financing and administration by a CRO is primarily utilized for drug, medical device and biologics research.[188] In the case of clinical research involving procedures, the cost of care for the subject may not be fully funded by federal grant funds.[189] The patient may require care for the underlying disorder regardless of their status as research subject for the experimental procedure. Typically, coverage and reimbursement will be sought from third party payers.[190]

Private Plan Coverage of Clinical Research: The Disappearing "Experimental" Exclusion

Traditionally, third-party payers, be they public or private, have had contract exclusions that deny coverage and reimbursement for experimental and investigational procedures.[191] These exclusions apply to reimbursement of unapproved drugs and devices, as well as provider reimbursement for performing experimental procedures.[192] If the experimental procedure is performed in a hospital and requires additional related services, the hospitalization and trial-related services may also be denied coverage and reimbursement.[193]

"Experimental" Exclusions: The Ambiguity Trap

Although health plan contracts typically exclude procedures or therapies that are considered "experimental" or "investigational," their

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[187]CROs do not generally have IRBs and indeed are discouraged from being involved in any way with the IRB for conflict of interest reasons. For example, an employee or consultant of a CRO would be a poor choice for membership on an IRB, either commercial or university based, given that projects managed by the CRO might be subject to that IRB's review and approval. *See* Kantra & Nasson, *supra* note 181, at 311-12.

[188]*See* IOM Report, *supra* note 11, at 23.

[189]For example, pharmaceutical and other private sponsors pay physicians for their work in a clinical trial at a substantially higher rate than do government grantors. For example, for oncology research, physicians get a median payment of $750 per patient from the National Cancer Institute, as compared to $2500 per patient for industry sponsored trials. *See* IOM Report, *supra* note 11, at 41-42.

[190]*See id.* at 30.

[191]*See generally* Angela R. Holder, *Funding Innovative Medical Therapy*, 57 ALB. L. REV. 795 (1994) (discussing insurance companies refusal to pay some or all of the charges relating to the care of a patient involved, however peripherally, in a clinical trial or other study).

[192]*See id.* at 795.

[193]*See id.* at 802.

subscriber contracts often struggle to adequately define these terms.[194] Health plan subscribers and beneficiaries may not even have a copy of the contract, having been given only a summary of the health plan, often referred to as the summary plan description.[195] When considering a dispute involving a health plan contract or summary plan description, any ambiguity in terms will be construed in favor of the non-drafting party, the subscriber or beneficiary.[196]

Absent a clear definition, a term like "experimental" will likely be found ambiguous and construed liberally in favor of the plaintiff.[197] For example, in *Taylor v. Blue Cross/Blue Shield of Michigan*,[198] the plaintiff, a thirty-five year old woman with advanced breast cancer, sought coverage for HDC/ABMT.[199] The insurer denied the claim citing a contract provision excluding services which were "experimental" or "research in nature."[200] The court held that both terms were ambiguous and noted that the plaintiff's experts, who had prescribed the therapy, testified it was not experimental but an effective form of therapy.[201]

In an effort to avoid ambiguity in contract clauses, many health plans have attempted to clarify terms related to experimental and investigational therapy exclusions.[202] Results have been mixed. For example, in one recent case,[203] the contract spelled out the specific conditions, including breast cancer for which "[a]utologous bone marrow transplant or other forms of stem cell rescue (in which the patient is the donor) with high dose chemotherapy or radiation [is] not

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[194]*See id.* at 796.

[195]*See* Martin v. Blue Cross & Blue Shield of Va., Inc., 115 F.3d 1201, 1202 (4th Cir. 1997).

[196]*See, e.g.*, Taylor v. Blue Cross/Blue Shield of Michigan, 517 N.W.2d 864, 867-68 (1994) (construing ambiguities in an insurance policy drafted by an insurer in favor of the insured); Lubeznik v. HealthChicago Inc., 644 N.E.2d 777, 780 (1994) (same).

[197]*See Taylor*, 517 N.W.2d at 868.

[198]*See id.*

[199]*See id.*

[200]*See id.*

[201]*See id.*

[202]*See, e.g.*, Bailey v. Blue Cross & Blue Shield of Va., 67 F.3d 53, 55 (4th Cir. 1995) (insurer's policy stated that "[a]utologous bone marrow transplants or other forms of stem cell rescue (in which the patient is the donor) with high dose chemotherapy or radiation are not covered").

[203]*See id.*

covered."[204] Although the exclusion with respect to the stem cell rescue was upheld by the court, the court found that the provision relating to the HDC portion of the procedure was ambiguous.[205] This was because chemotherapy was listed as a covered service elsewhere in the contract.[206] Thus, contrasting the two provisions, the court found the exclusion of coverage for the high dose version of chemotherapy to be ambiguous and unenforceable.[207]

Another method used by private health plans to clarify what falls within an "experimental" or "investigational" exclusion is reference in the contract to the specific criteria that will be used to evaluate a given procedure.[208] For example, United HealthCare, a large midwestern health plan, chose to avoid defining "experimental" by detailed exception language and instead opted for articulated, published criteria for evaluating whether a treatment would be considered "experimental."[209] The criteria were included in the contract and defined experimental exclusions as:

1) treatments not approved by the FDA to be lawfully marketed for that use, and not identified in the American Hospital Formulary Service, the AMA Drug Evaluation, or the Pharmacopoeia as an appropriate use;

2) treatment subject to review or approval by an institutional review board;

3) treatment that is subject of an ongoing clinical trial that meets the definition of a Phase 1, 2, or 3 clinical trial set forth in FDA regulations, regardless of whether it is a FDA trial;

4) treatment that has not been demonstrated through prevailing, peer-reviewed medical literature to be safe and

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[204] *See id.* at 53.
[205] *See id.* at 57.
[206] *See id.*
[207] *See Bailey*, 67 F.3d at 57.
[208] *See* Mark Holoweiko, *Experimental Treatment: Can You Do the Right Thing Without Going Broke?*, BUSINESS & HEALTH, May 1, 1995, at 38.
[209] *See id.*

> effective for treating or diagnosing the condition or illness for which its use is proposed.[210]

Blue Cross and Blue Shield Association also uses technology assessment criteria.[211] Its national technology assessment group offers evaluations of new therapies to the member plans to aid them in formulating coverage policy.[212] However, if the criteria are not incorporated into the beneficiary contract, they will be given short shrift by the court.[213]

Critics of such criteria-based systems argue that the physicians chosen by the plans to review the disputed technologies are biased by the financial incentives of denying care.[214] This criticism is countered by advocates of such criteria who note that physicians, who derive a highly remunerative livelihood from performing these procedures, and medical centers, which are increasingly profit-oriented, are just as likely to be swayed by financial incentives to provide this care.[215] Most

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[210]*See id.*

[211]*See id.*

[212]Several other large health plans also have the capacity to do technology assessment. *See* Merian Kirchner, *Who Pays For New Technology? Health Insurers are Thinking Twice About Coverage of High Tech High Priced Care*, BUSINESS & HEALTH, Oct. 1991, at 20. The Blue Cross and Blue Shield evaluation considers five factors:

1) Is the drug or device FDA approved for the medical indication in question?
2) Is there sufficient information in the peer reviewed medical and scientific literature to enable conclusions to be drawn regarding safety and efficacy?
3) Does the available scientific evidence demonstrate a net beneficial effect on health outcomes?
4) Is the drug, device, or treatment as safe and efficacious as existing therapeutic alternatives?
5) Can the drug device or procedure reasonably be expected to satisfy criteria 3 and 4 when applied outside the research setting.

See Pirozzi v. Blue Cross-Blue Shield of Va., 741 F. Supp. 586, 590 (E.D. Va. 1990).

[213]*See Pirozzi*, 741 F. Supp. at 590.

[214]*See* Holoweiko, *supra* note 208, at 38.

[215]*See id.* Demonstrating this phenomenon from an institutional perspective is a national chain of free-standing for-profit transplant centers operated by Response Oncology that provide high dose chemotherapy and stem cell transplants to advanced cancer patients. *See* Kolata & Eichenwald, *supra* note 24, at A6. *See also* Ann Saphir, *At the Center of Cancer Care: For-Profit Outpatient Centers Playing Bigger Role in Treatment, Clinical Trials*, MODERN

recently, there has been a movement on the part of payers and legislatures to develop external independent reviewer groups to review and adjudicate coverage disputes involving new technologies and treatments.[216]

Disputes regarding coverage gain a higher level of complexity in the context of self-insured Employee Welfare Benefit Health Plans, which, unlike traditional health insurers and plans, are governed by federal, rather than state law.[217]

Self-funded Health Plans and the Shifting Standard of Review

Self-funded health plans provide health care coverage for an increasing percentage of Americans.[218] In these plans, the employer self-insures, assuming the risk of loss for the health care claims of its employees.[219] These plans are governed by the Employee Retirement Income Security Act (ERISA) of 1974[220] and are susceptible to federal, not state law.[221] Indeed, ERISA preempts state laws, including state common law actions, that relate to such self-funded health plans.[222] For example, in

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HEALTHCARE, May 31, 1999 at 28 ("From 1996 to 1998, outpatient cancer centers doubled to 806").

[216]*See* Holoweiko, *supra* note 208, at 38.

[217]*See* 29 U.S.C. § 11332 (1994) (ERISA regulates self-insured Employee Welfare Benefit Plans).

[218]Between 107 and 120 million Americans with an employer provided health plan are covered under an ERISA plan; this is approximately 60 percent of those with employer-provided coverage. *See* HIAA, SOURCE BOOK OF HEALTH INSURANCE DATA 1997-1998, 33 (1998). The percentage of employers who choose to self-insure is steadily increasing. *See id.* Employers choosing to self-insure may do so under the Employee Retirement Income Security Act (ERISA). *See id.* ERISA provides employers with a series of advantages that result in administrative efficiencies, cost savings, and increased benefit design flexibility. *See id.* ERISA plans may contract with an insurer, third party administrator, or most commonly, managed care plan to administer the benefits and process claims, while the employer retains the risk of losses. *See id.* Such self-funded plans bear the risk of increased health costs directly. *See id.* The intermediary merely provides an "administrative services only" (ASO) product to the employer. *See id.*

[219]*See id.*

[220]*See* 29 U.S.C. § 11332 (1994).

[221]*See id.*

[222]A state law may be held to "relate to" ERISA plans if it affects an ERISA plan in any foreseeable way. So long as the state law has any "connection with" or "reference to" such plans, it will be preempted. Metropolitan Life Ins. Co v. Massachusetts, 471 U.S 724, 739 (1985). *Accord* Shaw v. Delta Air Lines, Inc., 463 U.S. 83, 96-97 (1983). Congress has

a recent Ninth Circuit case, *Bast v. Prudential Insurance Company*,[223] the court held that a widower's suit alleging a bad faith refusal to cover his deceased wife's HDC/ASCR was preempted by ERISA.[224] Despite being cognizant of the tragic facts, the court concluded that the plaintiff could seek no remedy under state law causes of action and was, therefore, left without a remedy.[225]

Under ERISA, significant deference is afforded the health plan with respect to interpretation of the plan and its scope.[226] However, in order to be granted such deference, the benefit plan must delegate discretionary authority to the plan administrator to construe the terms of the plan and determine benefit eligibility.[227] Generally, when a benefit decision is disputed, the court will engage in *de novo* review, ultimately construing any ambiguity in coverage terms in favor of the insured.[228] Under ERISA, *de novo* review serves as a default standard and is employed only when the plan has failed to definitively allocate to the plan administrator the authority to interpret the terms of the plan.[229]

Provided that the plan has explicitly provided the administrator with discretionary authority, the standard of review will be considerably more deferential to the plan than the default *de novo* standard.[230] Generally, fiduciaries are deemed to have abused their

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rejected "more limited" preemption language that would have been "applicable only to state laws relating to the specific subjects covered by ERISA." Moreover, a state law may "relate to" a benefit plan "even if the law is not specifically designed to affect such plans or the effect is only indirect." Ingersoll-Rand Corp. v. McLendon, 498 U.S. 133, 137-39 (1990). ERISA would not preempt a "generally applicable statute that makes no reference to, or...functions irrespective of, the existence of an ERISA plan." *See id.* at 139. In *Pataki v. Travelers Insurance Co.*, 514 U.S. 645, 664 (1995), the Supreme Court held that a surcharge placed upon hospital bills submitted to all payors except Blue Cross and Blue Shield, Medicaid, and HMOs had an insufficient nexus to the self-insured plans and was not preempted by ERISA.

[223]*See* Bast v. Prudential Life Ins. Co., 150 F.3d 1003 (1998).

[224]*See id.* at 1008.

[225]Under ERISA, the only remedy due to a plaintiff improperly denied benefits is equitable relief. There is no remedy under ERISA that provides for money damages. *See id.* at 1009.

[226]*See* Holder v. Prudential Ins. Co., 951 F.2d 89, 91 (5th Cir. 1995).

[227]*See* Glausner-Nagy v. Medical Mut. of Ohio, 987 F. Supp. 1002, 1011 (N.D. Ohio 1997).

[228]*See* Doe v. Group Hosp. & Med. Srvcs, 3 F.3d 80, 85 (4th Cir. 1993).

[229]*See* Firestone Tire & Rubber Co. v. Bruch, 489 U.S. 101, 115 (1989).

discretion "if they render decisions without any explanation, or construe provisions of the plan in a way that clearly conflicts with the plain language of the plan."[231] The court's role under this standard is limited to determining whether the administrator's "interpretation was made rationally and in good faith—not whether it was right."[232] Factors considered in determining "rationality" include the reasonableness or fairness of the decision-making, internal consistency of interpretations made by the plan administrator, and the factual background of the determination.[233]

Some courts have held that "less deference should be afforded to the decision of a plan administrator who is also a senior management official of the employer than is given to decision of an independent administrator" because of the "conflict of interest" inherent in the former's position.[234] This view has given rise to a growing movement toward using a "sliding scale" in assessing how much deference should be given an administrator in a dispute over benefits.[235]

Despite the barriers presented by ERISA, in recent years, use of the default *de novo* standard or other less deferential standard has been the rule rather than the exception in cases brought by plaintiffs seeking coverage for experimental procedures.[236] As a result, even in the context of ERISA plans, plaintiffs have been successful in obtaining coverage for HDC/ASCR.[237]

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[230]*See* Johnson v. Trustee West Conf. Teamster Pens. Trust Fund, 879 F.2d 651, 654 (9th Cir. 1989).

[231]*See id.*

[232]*See* Anderson v. CIBA-Geigy Corp., 759 F.2d 1518, 1522 (11th Cir. 1985).

[233]*See id.*

[234]*See* Kunin v. Benefit Life, 696 F. Supp. 1342, 1345 (C.D. Cal 1988). *See also* Judith C. Bostrom, *The Conflict of Interest Standard in ERISA Cases: Can it be Avoided in the Denial of High Dose Chemotherapy Treatment for Breast Cancer?* 3 DEPAUL J. HEALTH CARE L. 1, 14-18 (1999).

[235]*See* Chambers v. Family Health Plan Corp., 100 F.3d 818, 824 (10th Cir. 1996).

[236]*See e.g.* Bucci v. Blue Cross-Blue Shield, 764 F. Supp. 728, 729 (D.C. Conn 1991) (applying *de novo* review); Kulakowski v. Rochester Hospital Service Corp., 779 F. Supp. 710, 716 (W.D. N.Y. 1991) (same); Bailey v. Blue Cross & Blue Shield, 67 F. 3d 53, 56 (4th Cir. 1996) (same).

[237]*See, e.g.*, Bucci v. Blue Cross-Blue Shield, 764 F. Supp. 728, 732 (D.C. Conn 1991) (applying *de novo* review); Kulakowski v. Rochester Hosp. Srvc. Corp., 779 F. Supp. 710, 716 (W.D. N.Y. 1991) (same); Bailey v. Blue Cross & Blue Shield, 67 F. 3d 53, 56 (4th Cir. 1996) (same).

Litigation costs have prompted many employers and health insurers to abandon attempts to deny coverage for HDC/ASCR.[238] For example, despite the uncertainty surrounding the procedure, the Office of Personnel Management ordered the 350 health plans that cover federal employees to cover the procedure.[239] In 1996, a government study revealed that twelve out of twelve insurers contacted admitted that they were covering HDC/ASCR for breast cancer despite their belief that it was of unproven value.[240] They had tacitly decided to cover this therapy to avoid litigation, unfavorable press and legislative mandates.[241]

Health plans have found that the cost of denying coverage for controversial experimental therapies has a high public relations price tag.[242] Increasingly, the war over coverage of experimental therapies is waged not in the courts, but in the media.[243] Patients seeking experimental or novel therapies have found the media a more expeditious route of access to experimental therapy. As a result of high profile media attention and zealous advocacy by breast cancer support groups, coverage for HDC/ABMT or HDC/ASCR[244] for breast cancer has been mandated in several states.[245]

There is a distinct downside to the voluntary or mandated capitulation by health plans. In the case of the HDC/ASCR, there is

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[238] *See* GAO/HEHS 96-83, *supra* note 2.

[239] *See id.*

[240] *See id.*

[241] *See id.*

[242] *See id.*

[243] In the case of high dose chemotherapy and transplant, the media blitz has been aided by fears and hype about the dangers of managed care. *See, e.g.*, Michael Parrish, *It Could Happen to You*, HEALTH, May 15, 1996, at 20; *Do Managed Care Contracts Place You at Risk?* RN, Apr. 1, 1999, at 24; Michael Hiltzik, *Drawing the Line: an HMO Dilemma*, L.A. TIMES, Jan. 15, 1996, at 1; Tim O'Leary, *HealthNet Told to Pay $1 Million*, RIVERSIDE PRESS-ENTERPRISE, Oct. 18, 1995, at B01.

[244] Depending on when the provision was enacted, it may refer to the older HDC/ABMT procedure. the more recent HDC/ASCR procedure, or both

[245] Among these states are Kentucky (KY. REV. STAT. ANN. § 304, 38-1936 (Banks-Baldwin 1994)), Michigan (MICH. COMP. LAWS ANN. § 24 660 (416) (West 1993)), Minnesota (MINN. STAT. ANN. § 62A-309 (West 1996)), Missouri (MO. ANN. STAT. § 376.1200 (West 1991 & Supp. 2000)), Montana (MONT. CODE ANN. § 33-22-1521 (1998)), New Hampshire (N.H. REV. STAT. ANN. 415: 18-C (1998)), New Jersey, N.J. STAT. ANN. § 17:48-6k (West 1996)), Tennessee (TENN. CODE. ANN. § 56-7-2504 (1994 & Supp. 1999)), and Virginia (VA. CODE ANN. § 38.2-3418.1:1(Michie 1999)).

substantial concern that participation in trials and accrual of safety and efficacy information was actually hindered by payment extracted from third party private payers.[246] Indeed, reimbursement encourages the use of unproven technologies, and thus compounds the potential harms resulting from their premature use.[247] Recent concerns have focused on the reluctance of private health plans to deny care.[248] Health policy scholar Alain Enthoven argues that there "is an urgent need for managed care to second-guess decisions by physicians to subject patient to needlessly risky surgery and needlessly costly tests."[249]

Medicare Reimbursement of Services Associated with Clinical Trials

At the time Medicare was enacted in 1965, one of the standards that was borrowed from the private health insurance market was the requirement that care must be medically necessary and reasonable in order to be covered and reimbursed by Medicare.[250] Therapies and technologies that are "investigational" or "experimental" are not eligible for coverage.[251] Although this coverage policy is frequently articulated by Medicare, there is considerable uncertainty as to how concretely this exclusion is administered and maintained.[252]

In some cases, Medicare and the Health Care Financing Administration (HCFA) will study a new therapy or procedure and

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[246]One National Cancer Institute official stated that the recent breast cancer studies have shown that only good clinical trials can establish that a treatment works and that without adequate trials, patients and doctors "can be misled and progress against cancer can be hindered." Marilynn Marchione, *Advocacy Gets Ahead of Science in Battle Against Breast Cancer*, MILWAUKEE JOURNAL SENTINEL, Apr. 19, 1999, at 1.

[247]Performance of such experimental procedures outside of the clinical trial setting leaves patients unprotected by the stringent study review, informed consent requirements, and other human subjects protections applicable to legitimate clinical trials. *See* John H. Ferguson, *Court Ordered Reimbursement for Unproven Medical Technology*, 269 JAMA 2116, 2116 (1993).

[248]*See* Michael M Weinstein, *In Denial: Managed Care's Other Problem—Its Not What You Think*, N.Y. TIMES, Feb 28, 1999, at 10.

[249]*See id.*

[250]*See* 42 U.S.C. § 1395y(a)(1) (1994).

[251]This provision was explicitly spelled out in 1977 with Part A Intermediary Letter, No. 77-4, Jan. 1977.

[252]*See* Medicare Technology Assessment and Medical Coverage Decisions, GAO/HEHS 94-195FS (July 20, 1994).

issue a binding coverage decision.[253] For example, HDC/ASCR is not covered for treatment of solid tumors, such as breast cancer, under one such national coverage decision.[254] This decision was tested in the case of *Bosko v. Shalala*,[255] in which a plaintiff argued that the decision, issued in 1989, was no longer consistent with current technology and medical opinion.[256] However, the court noted that "legislators and judges are not medical specialists, and for that reason, it is necessary that administrative agencies develop and apply medical expertise."[257] The court refused to accept the plaintiff's contention that Medicare's decision to deny coverage was not based on "substantial evidence."[258]

The vast majority of Medicare coverage decisions are not the result of standard federal policy, but rather are interpretations made by fiscal intermediaries and carriers.[259] Moreover, HCFA has refrained from issuing explicit guidelines regarding what is reimbursable and what is not when the beneficiary is a subject in a clinical trial.[260]

Clinical research may result in a broad array of patient care services, most of which would be routinely covered by Medicare.[261] For example, a hospitalization for treatment of cancer would likely involve many services, in addition to the services or therapy that is provided under the research protocol. Inpatient care is generally paid under Part A of the Medicare Plan, using the diagnosis related group method of reimbursement.[262] In the normal course of billing, the charge for the hospitalization would be based on the discharge diagnosis, not a tallying and individualized review of each of the services provided.[263] The services provided by the physicians and other

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[253]*See id.* Note, however, that the Office for Technology Assessment has been discontinued and as a result, national coverage decision-making capacity is imperiled.

[254]Medicare covers autologous stem cell transplant for several malignant conditions, including leukemia. However, the policy specifically excludes coverage for solid tumors (such as breast cancer) with the exception of neuroblastoma. *See* Coverage Issues Manual—Medical Procedures 35-30, <http://www.hcfa.gov>.

[255]*See* Bosko v. Shalala, 995 F. Supp. 580 (W.D. Pa. 1996).

[256]*See id.* at 583.

[257]*See id.*

[258]*See id.*

[259]*See id.*

[260]*See* IOM Report, *supra* note 11, at 30.

[261]*See id.* at 54.

[262]*See id.*

[263]*See id.* at 30.

individual Part B providers are billed to Medicare on the resource-based relative value scale.[264] This is a fee-for-service system, so a service that would be normally covered, like a doctor visit, procedure or a lab test, would be reimbursed as usual unless the provider were to proactively exclude it as specifically related to clinical research.[265]

Indeed, regardless of what HCFA's initial intent might have been with respect to coverage of services connected with clinical research, it has found itself unable to discern when routine services, otherwise covered, are delivered to patients because of their participation in clinical trials.[266] According to a recent study published by the IOM, coverage and reimbursement of medical services—especially routine services—associated with clinical trials is common.[267] Indeed, the IOM sought to verify this "widespread understanding" with a study commissioned by the Lewin Group, a health policy consulting firm.[268] In the course of the study, clinical trial investigators reported that routine patient claims generated in clinical trials are routinely submitted and paid by plans.[269] This finding was sustained across a variety of research areas. For example, surveyed oncologists alleged that they bill third-party payers for both investigational and routine patient care services.[270] In many cases, a lack of clarity about what is the standard therapy contributes to the inability to draw a clear distinction between the two categories.[271] In fact, oncologists indicated that claims would be routinely submitted for nearly all the routine services used in the course of the clinical trial.[272] Similarly, cardiologists reported that they commonly bill insurers for routine patient costs in clinical trials, although not necessarily for protocol-specific procedure costs.[273]

In 1996, an audit revealed that most of the audited hospitals had billed Medicare for care rendered in connection with implantable

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[264] *See id.* at 34.
[265] *See* IOM Report, *supra* note 11, at 30.
[266] *See id.* at 30.
[267] *See id.* at 30-31.
[268] *See id.* at 38-40.
[269] *See id.* at 39-43.
[270] *See* IOM Report, *supra* note 11, at 39-40.
[271] *See id.* at 42.
[272] *See id.* at 39-40.
[273] *See id.* at 40-41.

medical devices.[274] Ultimately, HCFA chose to enter into an agreement with the FDA and cover a large percentage of investigational devices.[275] Indeed, investigational devices that fall into this covered category include 96 percent of the devices in ongoing clinical trials.[276]

HCFA has also engaged in a number of "coverage with conditions" arrangements designed to provide access to certain promising, still investigational, treatments being offered in "centers of excellence."[277] This was the method HCFA chose to employ when confronted with lung volume reduction surgery (LVRC).[278] Like the HDC/ASCR treatment for breast cancer, LVRC was hailed as a breakthrough treatment for patients with advanced emphysema.[279] Patients who had few other options embraced the surgery eagerly, despite the lack of research demonstrating its safety and efficacy.[280] Many, if not most, of these patients submitted claims to Medicare for coverage of the procedure.[281] Medicare made the decision to only cover the costs of this controversial therapy when it was administered in the context of an authorized clinical trial.[282]

In addition to the clinical trial costs that Medicare has chosen to assume, a 1997 Government Accounting Office report found that Medicare was reimbursing, albeit mistakenly, routine patient care costs sustained by patients in cancer clinical trial programs.[283] This report was further verified by information obtained by the IOM for its 1999 study.[284]

IOM researchers contacted Medical Directors of fiscal intermediaries and questioned them as to their reimbursement practices. The Medical Directors revealed "general recognition" that providers

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[274] *See id.* at 32.

[275] *See* IOM Report, *supra* note 11, at 33.

[276] *See id.* at 34.

[277] *See id.* at 36.

[278] *See* Coverage Issues Manual—Medical Procedures 35-93, <http://www/hcfa.gov>; Tonelli, *supra* note 7, at 35.

[279] *See* Tonelli, *supra* note 7, at 35.

[280] *See id.*

[281] *See id.*

[282] *See* IOM Report, *supra* note 11, at 36; Tonelli, *supra* note 7, at 35.

[283] *See* IOM Report, *supra* note 11, at 33.

[284] *See id.* at 39.

regularly submit claims for services provided in clinical trials and further noted that detecting such claims would be dependent on some inconsistency signaling participation in a clinical trial.[285] Interestingly, regardless of the established Medicare policy denying such claims, if they are detected, "no medical directors said they could flatly deny reimbursement for any and all patients in clinical trials."[286]

In summary, under both Medicare and private health plans, many of the routine costs associated with clinical trials are covered and reimbursed.[287] In many cases, reimbursement may be unwitting, due to an inability to differentiate between claims associated with clinical trials and those associated with other routine patient care.[288] In other cases, the private health plan or Medicare fiscal intermediary knowingly pays these costs, reasoning that many of the costs would have been incurred in caring for the patient regardless of the clinical trial.[289] In yet other cases, the plan seeks to avoid costly courtroom and/or media battles by succumbing to pressure to pay for an unproven therapy or procedure.[290]

None of these solutions, however appealing to researchers and patients seeking experimental procedures, address the question whether unproven therapies merit coverage in our increasingly costly health care system.

Who Should Pay and Why? Balancing Risks, Benefits and Costs

Current policy with respect to coverage and reimbursement of clinical trials does not contain explicit guidelines, even in the case of Medicare the largest single payer.[291] Explicit guidelines are desperately needed, not only by Medicare, but other payers, researchers and patients. The IOM recently issued a series of recommendations for an explicit Medicare coverage policy for clinical trials.[292] The IOM

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[285] *See id.* at 43-44.
[286] *See id.* at 43.
[287] *See id.*
[288] *See* IOM Report, *supra* note 11, at 43.
[289] *See id.* at 6.
[290] *See* GAO/HEHS 96-83, *supra* note 2.
[291] *See* IOM Report, *supra* note 11, at 30-32.
[292] *See id.*

recommendations argue for coverage of routine patient costs incurred in the course of clinical research, placing virtually the entire burden for these costs on third party payer.[293] This article proposes a slightly different strategy which would allocate costs of research to those who are most likely to benefit now and in the future.

The standard applied to funding of clinical research should seek to reflect the risks and benefits borne by those with a vested interest in study outcomes. Foremost among these are human subjects. Third party payers, be they public payers like Medicare, or private health plans, have less of a personal stake in research. Yet third party payers maintain a major role in covering the costs of health care, and, therefore, have a vested interest in improved health outcomes. Finally, those who fund research and researchers themselves are direct stakeholders in the research enterprise.

The Direct Stakeholders: Funders, Researchers and Providers

Research is largely funded by the federal government and private industry.[294] Federal funding is drawn from tax dollars. Private industry support of research is ultimately recovered by the pharmaceutical, device or other manufacturer through sales of the approved product to consumers.[295] Both private and public funders have a duty to finance research that will maximize individual and public health benefit while limiting risk.[296] This duty is woven into virtually every step of the research process.[297]

Federal funding agencies, such as the NIH, have dual concerns that the medical and scientific research they fund contributes to the health and safety of the public and also advances the frontier of science. To ensure this, they carefully review research projects, award dollars

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[293]*See id.* at 53-64.

[294]*See* Neumann & Sandberg, *supra* note 7, at 111.

[295]Pharmaceutical industry research and development spending as a percentage of U.S. pharmaceutical sales has risen from 11-12 percent in the 1970s to 21 percent in 1997. *See* Neumann & Sandberg, *supra* note 7, at 111. Typically private sector sponsors of clinical trials cover the costs of protocol-induced services, but do not provide money for routine patient costs. *See* IOM Report, *supra* note 11, at 7.

[296]*See* IOM Report, *supra* note 11, at 30-33.

[297]*See id.* at 30.

only to those judged worthy, and require adherence to human subject protections.[298] Private industry funders are usually pharmaceutical firms who, although they are economically motivated, are nonetheless bound by federal law to conduct research in a principled fashion that maximizes the safety of human subjects.[299]

Protection of human subjects and the duty to provide full disclosure is crucial to research funded by the federal government or private industry.[300] In the case of FDA regulated and federally funded research, protection of human subjects is fostered, but not absolutely ensured, by human subject protections and IRBs.[301]

Even when IRB approval has been obtained, human subject protections have proven inadequate on occasion.[302] For example, gene therapy research being conducted at the University of Pennsylvania recently resulted in the death of a young subject.[303] The subject, who had a genetic enzyme disorder that required dietary restrictions, was enrolled in a clinical trial that involved injecting a viral vector[304] carrying the missing gene directly into the liver.[305] Investigation of the subject's death revealed that the subject had not been an appropriate candidate for the study, and that the subject had been misled as to a likelihood of benefit, and that information regarding severe adverse reactions had been withheld.[306] This violation of research ethics and breach of standards resulted in the suspension of the University of Pennsylvania's gene therapy program.[307] Even more alarming than the

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[293]*See* Funding Health Services Research, *supra* note 92, at 93-96; SUGARMAN, *supra* note 93, at 33-34.

[299]*See* 21 C.F.R § 50 (1999) (codifying the "Common Rule" as applicable to research for products seeking FDA approval.)

[300]*See* 45 C.F.R. § 46 (1999).

[301]*See id.* Although the IRB is able to evaluate the study before it is undertaken and reevaluates it periodically, it does not directly monitor the study.

[302]*See* Rick Weiss & Deborah Nelson, *Gene Therapy's Troubling Crossroads: A Death Raises Questions of Ethics*, WASH. POST, Dec. 31, 1999, at A3.

[303]*See id.*

[304]*See* Stolberg, *supra* note 3, at A1.

[305]*See id.* The goal was for the gene to begin to synthesize the necessary enzyme once it had been imported into the subject's liver. *See id.*

[306]*See id.*; *Teen's Father: Gene Therapy's Risks Hidden*, CHICAGO SUN-TIMES, Feb. 3, 2000, at 23.

[307]*See* Jeffrey Brainard & D.W. Miller, *U.S. Regulators Suspend Medical Studies at 2 Universities*, CHRON. HIGHER EDUC., Feb. 4, 2000 at A30; Stolberg, *supra* note 3, at A1.

human subject lapses in this single case was the revelation that adverse reactions to experimental gene therapy, including deaths, had not been reported as required by law by researchers at Harvard.[308] Researchers, it is alleged, have been overzealous and cavalier, disregarding their duty to abide by the research protocol and comply with human subject protections.[309] The aftermath of the gene therapy debacle has reawakened Congressional interest in enhancing the protections accorded to human subjects.[310] But while federal regulations afford human subjects some protection in the United States,[311] research is an international enterprise; studies from other nations impact research and care in the United States.[312] For example, in the case of the HDC/ASCR research, much hope was vested in the South African study that had allegedly shown benefit.[313] This hope was quickly dashed, when it was revealed that, not only had the data been falsified, but the investigator had successfully duped the IRB in a South African University.[314]

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[308]*See* Deborah Nelson & Rick Weiss, *Gene-Therapy Deaths Belatedly Reported*, SEATTLE TIMES, Jan. 31, 2000, at A1, A11.

[309]*See id.* Moreover, this gene therapy research is doubly bound to comply with human subjects protection; the research involves a biotechnology product, regulated under the FDA, and was partially federally funded. *See id.*

[310]*See* Lisa Seachrist, *Senate Questions Oversight of Gene Therapy Experiments*, BIOWORLD Today, Feb. 3, 2000, at 30; Chris Adams, *Regulators Plan to Sharpen Watch Over Gene Therapy*, WALL. ST. J., Feb. 3, 2000, at B23.

[311]There has been much attention focused upon human rights issues in the context of experimentation. This has largely been a result of the atrocities of the Holocaust in World War II and other war-related research. *See* Kevin M. King, *A Proposal for the Effective International Regulation of Biomedical Research Involving Human Subjects*, 34 STAN. J. INT'L L 163, 167 (1998). However, much of this attention has focused on the theoretical, rather than the practical application of the well-recognized principles.

[312]For example, the HDC/ASCR breast cancer clinical trial included a total of five studies, only two of which were conducted in the United States. *See* ASCO, *supra* note 123. The study with falsified data was done in a South African University, which had an IRB in place. Nevertheless, they did not notice that the researcher had submitted falsified data until questions began to be asked. *See* Grady, *supra* note 148. Moreover, there are also questions as to how this bogus study was able to pass muster with the American Society of Clinical Oncology. When questioned as to their standards, a society official stated that the "group has rigorous scientific standards, but essentially used an honor system." *Id.*

[313]*See* ASCO, *supra* note 123 (abstract of Study #4). *See* Grady, *supra* note 148, at A7; Lauran Neergaard, *Studies on Breast Cancer Treatment Breed Debate—Of Five, One Finds Marrow Transplant Helps Women Live Longer, Other's Disagree*," ALLENTOWN MORNING CALL, Apr. 16, 1999, at A11.

[314]*See* Grady, *supra* note 148, at A7.

Additionally, researchers are increasingly susceptible to conflicts of interest.[315] As research is increasingly funded by private industry, it is becoming more dominated by profit motives as opposed to traditional academic values.[316] For example, the field of gene therapy has moved from a focus upon rare genetic diseases to cancer treatment.[317] Since cancer affects a greater portion of the population than rare genetic disorders, the development of cancer treatments inevitably results in the making of tremendous profits, far greater than profits resulting from treatment of a rare genetic disorder.[318] For example, Response Oncology, a for-profit chain providing HDC/ASCR brought in an impressive $128 million in revenues in 1998 alone, boasting a 15 percent profit margin.[319] Academic medical centers also have come to view their HDC/ASCR programs as the "cash cow for the cancer service."[320]

Scientists, who once shared results and sought collaborative consult, now must be mindful of the propriety interests of the funder of the research.[321] Moreover, scientists may share in that proprietary interest if they or their academic institution ultimately will share in the financial success of the final product.[322] In the University of Pennsylvania gene therapy program, the University was allied with several biotechnology companies that were involved in similar research.[323] One of the companies had been founded by a leading geneticist involved in the study that resulted in the subject's death.[324]

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[315]Critics express concern that gene therapy research is vulnerable to abuse because it is largely backed by venture capital. Researchers often are also investors. In their latter role, they may be tempted to oversell the promise of the experiments and keep knowledge of adverse events quiet so as not to depress stock price. *See Gene Therapy Run Amok*, WASH. POST, Jan. 29, 2000; Ellen Goodman, *Gene Therapy Need Government Reins*, NEWSDAY, Feb. 5, 2000, at B7.

[316]*See* Weiss & Nelson, *supra* note 301, at A3.

[317]*See id.*

[318]*See id.*; Saphir, *supra* note 215, at 28.

[319]*See* Kolata & Eichenwald, *supra* note 24, at A1. For example, in the aftermath of the breast cancer studies presented at ASCO, Response Oncology experienced a 23 percent decrease in revenue. *See* David Flaum, *Drop in High Dose Chemotherapy Cuts Response Oncology's Profits*, COMMERCIAL APPEAL, Aug. 13, 1999, at C2.

[320]*See* Kolata & Eichenwald, *supra* note 24, at A1.

[321]*See* Weiss & Nelson, *supra* note 301, at A3.

[322]*See id.*

[323]*See* Stolberg, *supra* note 3, at A1.

[324]*See* Weiss & Nelson, *supra* note 301, at A1; Stolberg, *supra* note 3, at A1.

Although the University and its researchers denied that their financial interests influenced their ardor for conducting the research or played a role in their skirting the human subjects protections, questions about researchers' motives have persisted.[325]

Researchers may also be corrupted by the quest for academic prestige and the all-important currency of academic publications.[326] For example, in the recent revelations regarding the falsified study on breast cancer, the researcher stated that he had engaged in the fraud "out of a foolish desire to make the presentation more acceptable to an audience."[327] Apparently he was seeking the affirmation and respect of peers when he boldly presented the falsified study at the American Society of Clinical Oncologists and basked in the glory of having produced the "ray of hope" for cancer patients.[328]

The situation becomes even more complex when the "researcher" is also a provider of the unproven therapy.[329] This is frequently the case when a therapy's "hype outpaces its hope."[330] The danger is exponentially increased when the therapy is a procedure not subject to federal regulations and not monitored by an IRB. In these instances, providers have demonstrated they are unlikely to critically review the innovative procedures that they recommend.[331]

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[325]One of those questioning the motives of the University of Pennsylvania researchers was the father of the subject who succumbed. In his testimony before Congress, the subject's father stated that both he and his son were misled by researchers, whose motivations were, in retrospect, suspect. Citing "money and fame" as goals in the "race for results," the father urged Congress to fortify the human subjects protections. *See* Weiss & Nelson, *supra* note 301, at A3.

[326]*See* Goodman, *supra* note 314, at B7 ("[T]he prize may be Nobel as well as financial").

[327]*See* Lauran Neergaard, *Scientist Falsified Data Supporting Cancer Regimen*, SEATTLE TIMES, Feb.5, 2000 at A2.

[328]*See* Grady, *supra* note 148, at A7.

[329]The reimbursement system rewards physicians for providing as many services as possible to their patients. *See* Jost, *supra* note 4, at 659.

[330]*See* Goodman, *supra* note 314, at B7.

[331]For example, in the case of lung volume reduction surgery, another unproven procedure with no evidence-based research supporting its use, numerous institutions and physician eagerly began to offer the procedure. Indeed, several centers began to recruit referrals using mass mailings. *See* Tonelli, *supra* note 7, at 35. Similarly in the case of the HDC/ASCR treatment for breast cancer, oncologists promoted the unproven treatment with complete impunity. Indeed even the American Society of Clinical Oncology was emphatically touting the therapy as superior as early as 1992. *See* Napoli, *supra* note 148.

Such is the case with HDC/ASCR. Seeking to supply a public demand, providers have administered this unproven therapy to thousands of patients outside of clinical trials.[332] They have billed third party payers for this therapy and refused treatment to patients unless they could guarantee payment.[333] Moreover, seeing an opportunity to exploit the patients and the payers, providers have launched highly lucrative for-profit ventures offering this unproven, risky therapy to these vulnerable consumers.[334]

In summary, funders of research have a vested interest in producing products and therapies that will maximize benefit and limit risks to the ultimate consumers. The federal government is motivated by its desire to better public health and safety. Private industry is motivated by the profit that will result from a safe, effective, marketable new treatment. Researchers' aims are more complicated. Some function as pure academicians while others seek to be entrepreneurs. This introduces numerous potential conflicts of interest. Researchers, then, may have a financial stake in the new product or device, either directly or through the research center or university.[335] Similarly the researcher may be swayed by a desire to impress his peers, build his academic reputation and win tenure and other accolades.[336] Those who provide unproven therapies, even in the context of "last best hope," do so for money or prestige, often without the approval of an IRB, and little, if any, accountability. Empathy for the patient may be but a secondary motive.[337]

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[332]*See* Neergaard, *supra* note 312, at A11.

[333]For example, patients requesting the therapy are typically asked to put their money on the table before they can qualify. For example, one press story recounted the saga of a young woman with breast cancer who received not one, but two HDC/ASCR procedures during her long battle with breast cancer. For the first one, she was required to pay $80,000, a very discounted rate because her husband was a physician on the hospital's staff. The second procedure, which required a six week hospitalization cost $280,000. Despite the fact that the care was not provided through a controlled study, the patient's health plan covered the cost. *See* Foreman, *supra* note 110, at B1.

[334]*See* discussion on Response Oncology centers, *infra* at p. 475.

[335]*See* Kolata & Eichenwald, *supra* note 24, at A1.

[336]*See* notes 318 & 319, *infra*, and accompanying text.

[337]*See id.*

The Unsteady Balance Between Patient Protection and Autonomy

Although patient autonomy is one of our most cherished ethical principles, it must be balanced with the need for carefully monitored protections in the context of clinical research.[338] Patients are often imbued with both an expectation of health care as a right and a belief that research always provides benefit to the subject. Neither of these assumptions reflect reality.

Federal regulations limit subject/patient access to drugs, devices and therapies until they are proven safe and effective.[339] This protection extends not only to the individual subjects but to society as a whole in that distribution of research products and therapies is limited until they are of proven quality and safety.[340] Violation of these laws and regulations will result in government censure with civil penalties and even criminal prosecution.[341]

In the case of FDA regulated products and research conducted under the NIH, the law strikes a balance between protecting subject patients and furthering research. Patients may seek to be subjects, and may even be paid to enroll in the study, but mechanisms are in place to protect them from exploitation and victimization by researchers.[342] This is not paternalism. It is recognition that patient/subjects in research are inherently disadvantaged as parties in highly technical and complex research projects.

Patient autonomy also is modulated in the context of how limited resources are distributed. For example, with regard to Medicare and

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[338]There is, for example, an entirely different ethic and flavor to informed consent in the context of research. In research, informed consent essentially focuses on emphasizing the unknowns of the experiment and on the fact that the subject cannot necessarily expect benefit. In traditional informed consent transactions, the goal is to disclose all of the known, material information to the patient, to aid them in making the most beneficial choice they can. *See* Tonelli, *supra* note 7, at 35.

[339]*See* Zujewski, *supra* note 120, at 200.

[340]*See id.*

[341]*See id.*

[342]*See* Neal Dickert & Christine Grady, *What's the Price of a Research Subject? Approaches to Payment for Research Participation*, 341 NEW ENG. J. MED. 137, 198 (1999). These mechanisms include informed consent, protocol review and evaluation by the grantor and the IRB, and full disclosure of risks and benefits, including the fact that the research may not benefit the subject directly. These protection are designed to enhance autonomy as well as protect.

Medicaid, regulations may limit what the autonomous patient may receive and when.[343] In private health plans, the employer or the insurance contract will limit the scope of coverage and the amount of reimbursement.[344] With both public and private payers, limitations on resources may limit patient access to certain services.[345]

What, then, happens when a patient demands access to an unproven experimental therapy? This situation has emerged in the context of cancer therapies like laetrile[346] and more recently with HDC/ASCR.[347] The patient often sees the experimental therapy as a last best chance.[348] Indeed, this view is often echoed by the provider offering the therapy.[349] Having employed all other available therapies without success, the patient is desperate for another alternative.[350] But satisfying a demand for this unproven treatment is fraught with unfavorable consequences, both for the individual patient and society at large.

The dying patient is in a vulnerable position and may be unable to objectively analyze the merits and appreciate the perils of the experimental therapy.[351] Moreover, this patient is easy prey for the

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[343]*See id.*

[344]*See id.*

[345]*See id.*

[346]*See* Wilson v. Traveler Ins. Co., 605 P.2d 1327 (Okla. 1980) (awarding lung cancer patient treatment in a coverage dispute over laetrile due to the ambiguousness of the contract exclusion clause). Laetrile was subject to much of the same zealotry as HDC/ASCR. No less than 21 states mandated coverage before it was finally discredited as a therapy for cancer. *See* Ferguson, *supra* note 246, at 2117 (discussing the laetrile controversy).

[347]*See* discussion *infra* at p. 481. Moreover, this is not unique to the United States. In Italy, a combination of hormones, vitamins and low dose chemotherapy for cancer treatment generates such public demand that 36 percent of Italian prime time news was devoted to discussions of the therapy. The therapy was understood to be ineffective and harmful. *See Study Reports DiBella Multitherapy as Ineffective,* CANCER TRIALS, <http://cancertrials.nci.nih.gov.>

[348]*See* Marilynn Marchione, *Advocacy Gets Ahead of Science in Battle Against Breast Cancer—Women Demand Stem Cell Transplants Before Clinical Trials Can Test Their Worth,* MILWAUKEE J. SENTINEL, Apr. 18, 1999, at A3.

[349]*See* Kolata & Eichenwald, *supra* note 24, at A6.

[350]*See id.*

[351]Indeed, some argue that terminally and/or desperately ill patients should be treated as a vulnerable class and accorded enhanced protections in the context of research. *See generally* D. Christian Addicott, *Regulating Research on the Terminally Ill: A Proposal for Heightened Safeguards,* 15 J. CONTEMP. HEALTH L. & POL'Y 479 (1999) (discussing treating terminally ill patients as a vulnerable class).

unprincipled, unscrupulous researcher[352] or the ignorant, eager-to-please, eager-to-make-a-profit provider.[353] In either case, allowing patients unfettered autonomy exposes them to a number of unnecessary risks.[354]

In the gene therapy experiments, there have been several deaths in addition to the young man in Pennsylvania.[355] Similarly, in the falsified HDC/ASCR breast cancer trial, the control group was given a lesser regimen of chemotherapy to produce the impression that HDC/ASCR was superior.[356] While the research university stated that no patients were harmed to its knowledge,[357] it stretches the bounds of credibility to believe that the control group's survival chances were not negatively affected. The human subject protection laws failed these patients.[358] The vulnerability of the patient/subject is exponentially increased when the patient receives an unproven therapy outside of the research context. These patients and their families are unprotected by the enhanced human subject protections associated with research. They are, in essence, "sitting ducks" for providers who proffer the therapy. For example, HDC/ASCR has been sought by legions of desperately ill women, either unaware of or unwilling to accept that the therapy is unproven.[359] In addition to proving valueless, now that more data is emerging,[360] this risk-ridden treatment may have had the effect of both shortening lives and destroying the quality of the limited time these patients had left.[361] In a significant percentage of these cases, doctors have failed their patients.[362]

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[352]For example, the risk of being in a study without adequate protections or in which the data will be falsified or altered. *See* discussion *infra* at pp. 474-77.

[353]*See* Kolata & Eichenwald, *supra* note 24, at A3.

[354]*See* Boodman, *supra* note 116, at Z12 (discussing case of Gail Reines).

[355]*See* Nelson & Weiss, *supra* note 307, at A1.

[356]*See* Waldholz, *supra* note 138, at B7.

[357]*See id.*

[358]In the aftermath, the discussion has focused on enhancing the protection and making them the laws and regulations even more protective to protect against such abuses in the future. *See* notes 302 & 307, *supra* and accompanying text.

[359]*See* notes 331 & 332, *supra* and accompanying text.

[360]*See id.*

[361]*See* Neergaard, *supra* note 326, at A2.

The uncontrolled access to unproven therapies like HDC/ASCR ultimately damages society at large. Because of premature use of HDC/ASCR, many more women received this dangerous unproven therapy than would have had it been subjected to traditional principled research.[363] Its unfettered use outside the research context derailed the research effort, and accrual of scientifically valid data was ultimately delayed.[364]

Indirect Participants in the Research Enterprise: The Third Party Payers

Unlike most other industrialized nations, the United States does not have universal access to health care services.[365] Other nations, in having to formulate a system to provide health care to all, have had to develop a consensus as to a reasonable package of benefits.[366] Unfortunately, we have not had the need or the discipline to follow this example. The consensus that currently exists with regard to the parameters of coverage is limited to Medicare, Medicaid and private health plans.[367] Over time, we have seen a trend toward inclusion with regard to preventive medical care, but little progress in other domains has been achieved.[368]

Health plans, whether public or private, seek to avoid paying for unproven or speculative treatments that are viewed as unnecessary.[369] The primary method of excluding such services is via "experimental" exclusion clauses.[370] On balance, these exclusions have proven feeble

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[362]Indeed if patients who are contemplating a procedure that is of unproven efficacy, the physician has a duty to inform them of its experimental nature. If the physician indicates that there is an unsubstantiated benefit, then the physician breached the standard of care with respect to full disclosure and informed consent. *See* Tonelli, *supra* note 7, at 35.

[363]*See* Zujewski, *supra* note 120, at 200-08; *See* Kolata & Eichenwald, *supra* note 24, at A6.

[364]*See* Zujewski, *supra* note 120, at 200-08. *See also* Tonelli, *supra* note 7, at 35 (discussing same phenomenon occurring in context of lung volume reduction surgery).

[365]*See* Inglehart, *supra* note 12, at 72.

[366]Even in these systems however, coverage disputes arise with respect to new treatments and technologies. *See* Jost, *supra* note 4, at 644.

[367]*See* notes 191-93, *supra*, and accompanying text.

[368]*See* discussion, *supra*, at pp. 471-73.

[369]*See* discussion, *supra*, at pp. 460-62.

[370]*See* notes 191-93, *supra*, and accompanying text.

in courts of law.[371] They have also resulted in public relations disasters when used to deny care to a pitiable beneficiary.[372] In recent years, payers, particularly in the private sector, have opted to cover the cost of these unproven therapies rather than engage in costly courtroom and media battles.[373] Furthermore, isolating costs associated with research from costs not associated with research is administratively difficult and costly.[374] Because of this difficulty, both Medicare and private payers pay for a large proportion of research related costs.[375]

Recently, there has been increasing willingness of third party payers to assume the costs of services, especially routine services associated with research.[376] Medicare currently covers routine patient care costs associated with research involving a "category B" investigational device.[377] Medicare also covers costs of research for certain new procedures subject to special conditions.[378] In addition, both the Department of Defense's TRICARE program and the Department of Veterans' Affairs cover medical costs associated with NCI cancer research trials.[379]

With regard to private payers, the American Association of Health Plans encourages its health plans to reimburse the routine costs of care associated with NIH sponsored trials.[380] Several plans, namely United Health Group,[381] Aetna-U.S. Healthcare,[382] and Blue Cross and Blue Shield have agreed to reimburse for care in cancer research trial conducted under the NCI.[383] Noteworthy, however, is the fact that

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[371]See discussion, *supra* at pp. 460-65. Courts err and order payment for not only unproven, but dangerous therapies. *See* Tonelli, *supra* note 7, at 35.

[372]*See* Weinstein, *supra* note 247, at 10.

[373]*See id.*

[374]*See* IOM Report, *supra* note 11, at 42.

[375]*See id.*, at 42-43.

[376]*See id.*

[377]*See id.* at 33-34.

[378]*See id.* at 36.

[379]*See* IOM Report, *supra* note 11, at 45.

[380]*See id*, at 46.

[381]*See Weighing the Cost*, BEST'S REVIEW—LIFE-HEALTH INSURANCE EDITION, Mar 1, 1999, at 40; *Clinical Trials: Promising Decision from New Jersey*, AM. MED. NEWS, Jan 31, 2000, <http://www/ama-assn.org/sci-pubs/amnews>.

[382]*See* Boodman, *supra* note 116, at Z12.

[383]*See* Terry, *supra* note 6, at 124.

many of these offers have not been accepted.[384] But this avowed willingness of payers to cover research costs begs the question of whether our public and private payers *should* be paying for clinical research.

Balancing the Risks and Benefits with the Responsibility to Pay

Parties in the research enterprise have conflicting interests, and the risks and benefits of research are not evenly spread among the participants. Given those circumstances, those who benefit the most should be responsible for the majority of the cost, and those who assume the most risk should be absolved from covering the cost.

In the case of pharmaceutical and device research, private industry should cover the costs associated with research, because ultimately they will make a profit from the product. Subjects in pharmaceutical and device clinical trials assume the risk of treatment with an unproven experimental modality. In a Phase III trial, they also bear the risk of not receiving the new therapy if they are in the control group. Most subjects will not realize any personal health benefit from participation in the trial. Because of their contribution in term of risk-bearing, subjects should be insulated from the costs associated with research. However, society at large will benefit from safe efficacious products. Therefore, it is reasonable for third party payers to cover routine patient costs incurred during a clinical research trial, even when the research is funded by the private sector. Many of the these routine costs would have been incurred by the patient/subject for treatment of their underlying disorder in any case. Thus, the payer in most cases is assuming, at most, only a nominal increase in costs.[385] Moreover, since

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[384]Attempts of health plans to funnel patients to appropriate clinical trials have been rebuffed. United HealthCare reports that few patients have chosen to enroll in the trials, despite the willingness of the HMO to cover the costs. *See* IOM Report, *supra* note 11, at 46; Marchione, *supra* note 245, at 1. One health plan attempted to refer a breast cancer patient to a clinical trial, but was almost immediately countered with a threat of suit. *See* Holoweiko, *supra* note 208, at 38. The patient's attorney argued that the randomized clinical trial was no better than a "lottery ticket" and received major press coverage. *See id.* The health plan chose to pay rather than go to court. *See id.*

[385]Several studies have found the cost of participation in trials only marginally higher than the costs of patient care outside of the trial. For example, a study done at the Mayo Clinic found only a 3–13 percent increase in cost of care for patient in a trial. Similarly, a study done

much of research is funded either by federal tax dollars or revenue from product sales to the public, coverage of the costs of research is consistent with rather than contradictory to the public interest. In fact, the IOM has recently recommended that Medicare cover such routine patient costs.[386]

The long-range public benefit argument, however, is not as persuasive where private health plans are concerned. Private health plans sell a product that is price-dependent and subject to intense competition.[387] The private health plan usually has a fiduciary duty to its employer client to contain costs in the present, rather than devote resources to research whose benefits will come to fruition in the distant future. The employer is seeking or financing a product that cares for its workforce today in the most economical and comprehensive fashion. When additional coverage is added or mandated, the net result will be increased premium costs that may cause employers and individuals on the margin to not purchase coverage, thereby increasing the number of uninsured.

However, even in the context of private health plans, there is benefit inherent in improved therapies sufficient to warrant their assuming the burden for the routine patient care costs associated with clinical research. This assumption of routine patient costs should not be extended to cover the cost of the experimental device or drug, however. That cost should be borne by the manufacturer who will ultimately profit from the new therapy.

Research involving procedures presents more complex issues, from monitored NIH trials conducted by principled researchers[388] to uncontrolled use of unproven speculative treatment offered by overeager providers in an increasingly entrepreneurial health care industry.[389] In the former case, risks and benefits are distributed in the same way as in the case of pharmaceutical research. Here however, the downstream profits will be made by the providers of this therapy once

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with the Kaiser Permanente plan found only about a 10 percent differential. *See* IOM Report, *supra* note 11, at 26.

[386] *See id.* Medicare already covers these routine patient costs in the context of most investigational devices. *See* discussion, *supra*, at p. 472-73.

[387] *See* discussion, *supra*, at p. 459-61.

[388] *See* discussion, *supra*, at p. 448-49.

[389] *See id.*

it is part of the established treatment regimens. In addition, they will also win academic kudos for the publications the research produces. In the case of a federally or privately funded clinical trial, the provider may realize compensation through the funding and salary support provided by the grant. However, commensurate with the benefits they will receive in the foreseeable future, researchers should be foreclosed from seeking coverage from third party payers for performing the experimental procedure. Once again however, public policy is served by having payers cover other routine patient costs incurred. And once again, the patient who is the ultimate risk-bearer should be insulated from research-related costs.

The recent IOM report has recommended that research procedure costs should be paid for by Medicare when the procedure is done in a randomized trial, equivalent to a phase III trial in the pharmaceutical context.[390] This however unfairly rewards providers for engaging in research, and provides a financial incentive for premature use of unproven, but remunerative, procedures. Moreover, it is out of synchrony with the policy with respect to pharmaceuticals, where such premature windfalls are eschewed and human subjects protections are enhanced by FDA requirements.

Finally there is the problematic category of research that is not research at all, but rather use of an unproven therapy or speculative procedure in a traditional provider-patient transaction. There is no public health benefit here. Indeed, one can argue that patients may be unnecessarily put at risk by cavalier use of unproven therapies. The integrity of legitimate research is subverted by premature unprincipled use of an unproven procedure. The progress of legitimate research may be delayed, and harm to patients is likely, if not inevitable.

Patients, no matter how much they want the unproven procedure, are in a poor position to judge safety and efficacy. Often they are desperate, vulnerable patients offered a "last best hope" by a provider who has not necessarily critically reviewed the science. This is not quality medical care, nor is it respectful of patients. In the worst possible scenario, the patient is offered this therapy by a provider who,

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[390] *See* IOM Report, *supra* note 11, at 56-57.

though cognizant of the uncertain benefit, seeks to realize a profit by performing an expensive procedure.

There is no valid reason for third party payers, public or private, to be a party to this exploitation of patients. In the case of the public payers, there is no downstream public good that merits the use of tax dollars. Similarly, reasons for private health plans to pay for unproven procedures performed outside the research context are virtually nonexistent. In fact, in the case of both public and private payers, there is a duty to *not* pay for this exploitation of patients.

CONCLUSION

There is a broad spectrum of innovation that is frequently referred to as research. In reality, however, legitimate clinical research is limited to interventions that are undertaken in the furtherance of science and medical progress, where the benefit will usually not be experienced by the subject. This often is at odds with the subject's perception that he/she will realize some, at least marginal, benefit. A researcher's duty is to clarify this fundamental issue when recruiting and obtaining a subject's consent. In the course of legitimate research, subjects should be insulated from costs. Routine patient care costs should be absorbed by third-party payers and research-related costs should be borne by the party who will realize benefit when the drug, device, biologic or procedure has become the standard of care. These research protocol-related costs are properly allocated to the pharmaceutical or device manufacturer or, in the case of procedure research, to federal or other funding entity, researcher/provider, and institution sponsoring the research.

Unfortunately, most of the criticisms of inadequate funding for experimental therapies do not ultimately reflect concerns about legitimate clinical research. Rather, they concern innovative, unproven therapies sought by patients and providers who are out of options in treating a terminal or incurable disorder. Patients present a compelling and sympathetic case: they are suffering, usually dying, and will take any "last best hope." But, their argument for a last chance does not justify holding the health care system and it resources hostage, nor does it justify sacrificing the opportunity for legitimate clinical research and adequate study of the innovation prior to marketing. This is precisely

what has occurred in the case of both the HDC/ASCR treatment for breast cancer and LVRC for emphysema.

While patients present a sympathetic, albeit unsupportable case regarding unproven treatments, providers are far less sympathetic. "Patients may be easily persuaded by glowing reports of dramatic medical breakthroughs, but physicians...should know better."[391] Physicians have a duty to refrain from offering innovative, unproven therapies to patients outside a legitimate clinical trial. Physicians are the most likely to open the door to a new therapy, but are also the best equipped to close the door. Rather than engaging in a "dance of denial"[392] with the vulnerable patient, physicians owe patients honest, well-researched and critically reviewed assessments of treatment possibilities. Unfortunately, there will be situations where no viable treatment option exists.

Providers should be foreclosed from accessing third-party reimbursement for unproven therapies outside the confines of legitimate clinical research. Aside from the obvious misallocation of limited resources, there are profound conflict of interest questions.[393] Absent coverage and reimbursement, there is substantially less chance of unproven therapies being unleashed on the unsuspecting and needy market. Society does not tolerate such irresponsibility from pharmaceutical firms, and, likewise, should not tolerate it with respect to procedures and other treatments. To continue to do so will ultimately cause greater harm to greater numbers of patients, waste increasingly limited resources, further undermine the medical profession's ethical standards, and diminish the integrity of research.

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[391] *See* Tonelli, *supra* note 7, at 35.

[392] *See* Goodman, *supra* note 314, at B7.

[393] It is perhaps ironic that the financial conflict of interest question has been aimed primarily at health plans rather than at institutions and providers eager to offer unproven therapies for profit. *See* discussion, *supra*, at p. 475-78. In the case of provider conflicts, motivating profit may be direct, as in the case of Response Oncology, *see id.*, or indirect, as in using the unproven therapy as a "cash cow" to offset less profitable therapies, *see* Kolata & Eichenwald, *supra* note 24, at A6.