

2000

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Recommended Citation

James T. O'Reilly, *Elders, Surgeons, Regulators, Jurors: Are Medical Experimentation's Mistakes too Easily Buried?*, 31 Loy. U. Chi. L. J. 317 (2000).

Available at: <http://lawcommons.luc.edu/lucj/vol31/iss3/2>

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Elders, Surgeons, Regulators, Jurors: Are Medical Experimentation's Mistakes Too Easily Buried?

*James T. O'Reilly**

I. INTRODUCTION

The rise in both the population and health care needs of elderly Americans has created a booming market in surgical and pharmaceutical responses to illnesses associated with aging. To reach this market, manufacturers must prove to government agencies that their products are safe and effective for human use. The medical research industry spends about four billion dollars each year to link physicians, nurses and patients to the experimental products of manufacturers in order to achieve product approvals and to cure or prevent disease.¹

Because conventional medical research primarily is performed with healthy adult subjects between the ages of twenty-one and forty-five, medical device and drug developers are limited in their ability to predict the effects of new devices and drugs on the elderly.² Under recent directives of the Food and Drug Administration ("FDA"), an increase in the amount of human experimentation on elders is anticipated.³ While this trend carries the promise of better therapy for many, it also carries risks for the individual patients on whom these experiments are

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1. This estimate includes government-sponsored and manufacturer-sponsored drug and device research, with the industry sponsoring an estimated 75% of clinical research. See OFFICE OF INSPECTOR GENERAL, U.S. DEPT. OF HEALTH AND HUMAN SERVICES, INSTITUTIONAL REVIEW BOARDS: PROMISING APPROACHES, NO. OEI-01-97-00191 (1998) [hereinafter OIG REPORT, PROMISING APPROACHES]. This report is available at <<http://www.dhhs.gov/progorg/oei/reports/9274.pdf>>.

2. This issue is recognized in specific labeling requirements for prescription drugs where clinical studies did not include sufficient numbers of elderly subjects to adequately determine the effect the drug may have on an elderly patient. See 21 C.F.R. § 201.57(f)(10)(ii)(A) (1999).

3. See Guidelines on Studies in Support of Special Populations: Geriatrics, 59 Fed. Reg. 39,398 (1994); Guidelines for the Study of Drugs Likely To Be Used in the Elderly, 55 Fed. Reg. 7777 (1990).

performed. This Article examines the legal system's contributions to patient protections for elders and suggests that current systemic flaws be remedied by a comprehensive overhaul of patient protection legislation. Patient protection, in this context, involves the legal system actively discouraging unsafe or excessively risky pharmacological or surgical treatments.

II. UNDERSTANDING MEDICAL EXPERIMENTATION

A. *Defining Terms*

This Article defines the elderly as persons over sixty-five years of age, in accordance with FDA guidelines.⁴ Although many elderly persons are healthy and active, both law and regulation recognize the adverse effects of aging. These adverse effects include changes in the body's ability to excrete drugs (resulting in heavier accumulated doses) and in increased frailty of bones and internal organ systems.⁵

The phrase "human clinical studies" sounds impressive and suggests thousands of sick patients eagerly volunteering for a university's landmark research for a cure. In practice, studies are diverse in size, scope, motivation, setting and purpose. The original context of medical research was a crusading physician's efforts to learn from repeated patient experiences about a disease or condition that defied then-current therapies. The experimenter worked with her patients to find new ways to treat the health problem, then published the resulting data in medical journals to advance the knowledge of that condition and its most recent successful responses. Today, however, medical researchers can earn up to one million dollars a year for performing clinical research⁶ that is first held as the confidential property of a product sponsor⁷ and is later submitted to the FDA with a product approval application.⁸ Researchers can earn an average of \$2500 per patient for conducting clinical trials for the drug industry.⁹

4. See Draft Guidance for Industry on Content and Format for Geriatric Labeling, 64 Fed. Reg. 3302 (1999).

5. See Guidelines on Studies in Support of Special Populations: Geriatrics, 59 Fed. Reg. 39,398 (1994) (stating medical reasons for the classification); JAMES T. O'REILLY, *THE LAWYER'S GUIDE TO ELDER INJURY AND ACCIDENT COMPENSATION* (1995) (providing an overview of legal issues).

6. See Kurt Eichenwald & Gina Kolata, *Drug Trials Hide Conflicts for Doctors*, N.Y. TIMES, May 16, 1999, at A34.

7. See 21 C.F.R. § 312.130(a) (1999).

8. See *id.* § 314.1-.560 (detailing procedures for applying for FDA approval of a new drug).

9. The physician investigator's cost of enrolling and keeping a patient in a clinical trial aver-

For the purposes of this Article, four types of experiments on new medical products are considered “clinical research”:¹⁰ (1) experiments on ingestion of drugs and vaccines; (2) surgical implantation of medical devices; (3) medical procedures using electronic products such as computer-assisted tomography scanners and X-ray devices; and (4) surgical processes or methods in operations on the body using drugs, devices or other novel techniques. “Research” means that the primary medical purpose for treatment is a statistical evaluation of the effectiveness of the treatment or cure, not for the alleviation of a particular patient’s illness.¹¹ Treatment of an individual patient, on the other hand, is not research,¹² but such treatment may generate interesting observations worthy of notice and capable of being reproduced by other experimenters.¹³ The accumulation of those observations can provide helpful information about a prospective cure or treatment, but is more often merely anecdotal evidence rather than scientifically verifiable research data.

The fourth category of medical research, the methods and instruments of surgeons, is virtually unregulated for reasons discussed later in this Article.¹⁴ In the case of surgery, progress is made by experimental changes to conventional surgical techniques, for example, heart valve or liver surgery modification. The resulting variations are then reported in journals and may lead other surgeons to try the same type of procedure. Critics have called for better protections of surgical experimentation patients.¹⁵

ages \$2000 per person. The industry pays an average \$2500 per patient, while the National Cancer Institute pays \$750 for the same type of clinical research effort. *See Few Take Part in Cancer Tests, Slowing Research, Survey Finds*, N.Y. TIMES, May 16, 1999, at A32 [hereinafter *Few Take Part in Cancer Tests*].

10. *See* 21 C.F.R. § 312.3(b) (1999) (defining clinical investigation as experimentation with humans).

11. *See id.* (excluding treatment from the investigational regulations of the FDA).

12. *See Doe v. Sullivan*, 756 F. Supp. 12 (D.D.C. 1991), *aff’d*, 938 F.2d 1370 (D.C. Cir. 1991).

13. *See* 1 NATIONAL BIOETHICS ADVISORY COMMISSION, RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY, at 6 n.34 (Dec. 1998) [hereinafter NBAC] (exploring the distinction between the research conducted on patients for statistical evaluation and extraordinary treatment of individual patients, which does not constitute research).

14. *See infra* Part VII.J (discussing the FDA’s limited jurisdiction over surgeons).

15. *See* R. Alta Charo, *Human Subjects Have it Worse Than Guinea Pigs*, 46 CHRON. OF HIGHER EDUC., June 25, 1999, at A64.

B. Performers of Clinical Research

Medical research has undergone tremendous change in the 1990s. The bulk of human clinical research in drugs and devices is now conducted outside academic medical centers in settings such as individual doctors' offices.¹⁶ Sponsors of drugs and medical products and devices pay for nearly three-quarters of the human clinical research done in the United States¹⁷ because these sponsors have a legal duty to test their products adequately before marketing them to consumers and physicians.¹⁸ Drug development costs, however, are so monumental that strong economic incentives have pushed research work into lower-cost venues. This Article explores the legal fallout from this historic shift.¹⁹

American clinical research has moved from regarding academic medical centers as optimal medical research sites toward the use of for-profit study management organizations ("SMOs"), a category that includes clinical research organizations ("CROs"), which provide part-time testing venues and independent physician-run testing sites.²⁰ Research done under federal National Institutes of Health ("NIH") grants is still largely performed at academic sites. For commercially-funded research, however, there has been a dispersion of clinical testing to a variety of non-academic sites that do not have the costly infrastructure of teaching institutions.

Drug and device clinical research can be very lucrative for researchers.²¹ The NIH funds research projects at thousands of facilities and allows reimbursement of up to twenty-six percent of the research cost to cover the facility's administrative overhead.²² In the FDA

16. See Kurt Eichenwald & Gina Kolata, *A Doctor's Drug Studies Turn Into Fraud*, N.Y. TIMES, May 17, 1999, at A1.

17. See OIG REPORT, PROMISING APPROACHES, *supra* note 1, at A-1 n.3.

18. See *Tinnerholm v. Parke-Davis & Co.*, 285 F. Supp. 432 (S.D.N.Y. 1968), *aff'd*, 411 F.2d 48 (2d Cir. 1969).

19. See *infra* Parts VI, VII.H (discussing the possibility of dual tier testing as a result of the performance of medical research outside academic centers and noting the "finite boundaries" of the regulatory system).

20. See *infra* Parts VI, VII.H.

21. See *Few Take Part in Cancer Tests*, *supra* note 9, at A32 (noting that payment may be as much as \$2500 per patient).

22. "Overhead" includes indirect costs for facilities and the administrative management of clinical trials by the institution. See, e.g., National Institutes for Health, NIH Grants Policy Statement (1999), available at <http://www.grants.nih.gov/grants/policy/nihgps/part_iii_4.htm> (providing a policy on financial provisions for the costs associated with performing research under grants). The percentage of overhead permitted by an institution, however, is limited. See OFFICE OF MANAGEMENT AND BUDGET CIRCULAR A-110, UNIFORM ADMINISTRATIVE REQUIREMENTS FOR GRANTS AND AGREEMENTS WITH INSTITUTIONS OF HIGHER EDUCATION,

context, the SMOs and the clinical study placement coordinators who manage studies for drug and device manufacturers pay handsomely for access to patients who are likely candidates for the drug or device being tested.²³ In the face of health care cost reductions elsewhere in their budgets, more physicians and physician practice groups are now practicing some clinical research to boost profits. In fact, over one-half of the clinical studies of FDA-regulated drugs involve investigators outside of academia.²⁴

This Article examines one consequence of the shift away from academic venues and explores whether the change may present greater risks to patient protection goals.²⁵ An academic medical center protects its prestige and maintains its reputation by close internal adherence to norms of research quality.²⁶ For its adherence to these norms, an academic institution charges drug sponsors an overhead cost that exceeds what the individual physician's clinic would impose for the same statistical data of patient results.²⁷ The absence of an academic institution's compliance regimen may leave patients vulnerable to cost pressures, including the pressure to enroll patients who should not receive the drug or device in the study.

From the federal government's viewpoint, auditing records of patient protections like informed consent²⁸ and protocol monitoring is easier at larger academic institutions because there are numerous sources of information from which to verify and validate the procedures performed. Typically, a university or large teaching hospital will have an institutional review board ("IRB") that screens research before it is performed at the facility. IRB approval is, by federal regulation,²⁹

HOSPITALS, AND OTHER NON-PROFIT ORGANIZATIONS.

23. See Eichenwald & Kolata, *supra* note 6, at A34.

24. See Telephone Interview with Bette L. Barton, CDER Div. Sci. Investigations, Food and Drug Administration (July 20, 1999) [hereinafter Barton Interview].

25. See *infra* Parts VI, VII.G (noting the dissolution of the presumptive mechanism of institutional controls as medical research moves out of academic centers and the weakening of patient protections as clinical testing moves to scattered sites).

26. The failure to adhere to the norms of quality research results in a risk that studies may be suspended for inadequate institutional controls upon research. See, e.g., Jeffrey Brainard, *Watchdog Agency Blocks New Human-Research Projects at U. of Illinois at Chicago*, 47 CHRON. HIGHER EDUC., Sept. 10, 1999, at A44 (discussing the halting of new research on human subjects at the University of Illinois at Chicago).

27. The end point includes tabulated data demonstrating that the drug or device is effective and safe when compared to other therapies or a placebo. The absence of such data may defeat a new drug application. See 21 C.F.R. § 314.125 (1999).

28. See 45 C.F.R. § 46.116 (1998) (explaining the general requirement for valid informed consent).

29. See Institutional Review Boards, 21 C.F.R. § 56.103 (1999) (establishing IRB require-

required for research that will be submitted to regulatory agencies,³⁰ and is at least nominally required by the editors of scientific journals as a precondition to publication.³¹ The cases of fraudulent research that have been prosecuted in recent years³² suggest that smaller research sites' lapses of attention to patient protections have placed some patients at risk.

C. *How Research Results Are Communicated*

Results of human clinical research are reported in two very dissimilar venues. They are reported in either scientific journals, which emphasize wide dissemination of technical knowledge, or in applications for the approval of new drugs or devices, which are commercially driven. The peer review process for scientific journals involves examination of the research by experts in a particular field who ask questions and independently agree that the data and methods appear to be accurately described.³³ Publication, then, allows for further discussion by practitioners and rebuttal or verification in other hospitals or laboratories. For the most part, research funded by government grants or university funds is disseminated through scientific journals at the time and to the degree chosen by the individual medical researcher and the journal's editors.³⁴

The other venue for the reporting of human clinical results is the product-specific applications for regulatory approval, such as the New Drug Application³⁵ to the FDA and its counterpart applications for vaccines and medical devices.³⁶ In this context, the objective of the research is to win specific product approval of a potentially profitable medication or medical-use product. To assure a profitable return on the

ments).

30. *See id.*

31. *See* Robert Amdur & Chuck Biddle, *Institutional Review Board Approval and Publication of Human Research Results*, 277 JAMA 909, 913 (1997).

32. *See, e.g.*, *United States v. Garfinkel*, 822 F. Supp. 1457 (D. Minn. 1993), *rev'd*, 29 F.3d 451 (8th Cir. 1994) (reversing a dismissal of criminal counts for failure to follow investigational record keeping protocol); *United States v. Smith*, 740 F.2d 734 (9th Cir. 1984) (finding that clinical investigators submitted false statements, but not imposing criminal liability); *see also* 1 JAMES T. O'REILLY, *FOOD AND DRUG ADMINISTRATION* § 8.14 (2d ed. & Supp. 1999) (discussing additional unreported cases).

33. *See, e.g.*, National Institutes for Health, NIH Grants Policy Statement (1999), available at <[http://www.grants.nih.gov/grants/policy/nihgps/part_i.htm#peer rev](http://www.grants.nih.gov/grants/policy/nihgps/part_i.htm#peer%20rev)> (noting the "dual review system" used by the NIH).

34. *See id.*

35. *See* 21 C.F.R. § 314 (1999).

36. *See id.* § 812.20.

research investment, the applicant prepares its data in the mandatory format described in federal agency regulations,³⁷ then submits the package of research data, complete with summaries and analyses of research results. The primary goal in the filing of this data, unlike grant-funded research, is maintaining the secrecy of the results in order to preserve the expected profit potential of the invention.³⁸ The existence of the research itself is quite often held as confidential business data,³⁹ except where statutes require the publishing of lists of experimental sites for diseases such as AIDS.⁴⁰

D. *The Speed of Research*

Urgency in medical research has three underlying causes. In some studies of life-saving or medically important “breakthrough” products, the speed of research relates to the critical need to get the product to dying patients. The very successful comparative drug study, for example, might end earlier than expected out of ethical concern for study participants who did not receive the actual beneficial medicine once the benefits of the experimental product become overwhelmingly clear. FDA product approval can be sought on the “fast track,” which is a special regulatory process for drugs for the most life-threatening diseases.⁴¹ The fast track shortens the time for the FDA data review and waives the normal sequence of additional human experiments. As a result, the process may produce market clearance for an extremely important therapeutic breakthrough drug in a matter of a few months.

A second cause of urgency is the classic scientific competition in which experts formulate rival hypotheses, conduct research and publish results before competing experts can complete their work. The hope, of course, is that the publication of these results will earn prizes and acclaim for the institution and the researchers. This very conventional

37. *See id.* § 314.50.

38. *See* 21 U.S.C.A. § 331(j) (West 1999); *Public Citizen Health Res. Group v. FDA*, 185 F.3d 898 (D.C. Cir. 1999); 21 C.F.R. § 314.430 (1999).

39. *See, e.g., Public Citizen Health Res. Group*, 185 F.3d at 904-06 (demonstrating how this confidential status has received judicial support in Freedom of Information Act case law pursuant to 5 U.S.C. § 552(b)(4)); *Citizens Comm’n on Human Rights v. FDA*, 45 F.3d 1325, 1328 (9th Cir. 1995) (finding data protected as exempt); *Anderson v. Department of Health and Human Services*, 907 F.2d 936, 942 (10th Cir. 1990) (giving less deference to FDA exemption decisions); *see also* James T. O’Reilly, *Knowledge is Power: Legislative Control of Drug Industry Trade Secrets*, 54 U. CIN. L. REV. 1, 14-20 (1985) (discussing the intense legislative debates that led to the confidential status of this data).

40. *See* 42 U.S.C. § 300cc-17(e) (1994).

41. *See* 21 C.F.R. § 314.510 (1999) (providing for the accelerated approval of new drugs that treat serious or fatal illnesses).

competition intersects little with the regulatory system, though the researcher's competitive zeal may be a basis for a claim of negligence if a patient harmed by shortcuts in research sues in tort.⁴²

Finally, a third cause of urgency is the financial pressure on medical device companies and the surgeons who serve as their product investigators to rapidly develop the data that shows the device to be effective and ready for approval by the FDA.⁴³ When this sense of urgency stimulates surgical activity, the FDA has more difficulty overseeing such actions in the operating room. It is easier for regulators to track the dispensing of medications and the charts of patients' responses to doses of different drugs.

Urgency has the patent law advantage of taking a primary position for the innovator who patents a device first. For FDA-regulated drugs and devices there is also the quasi-patent benefit of exclusivity for a statutory period of time.⁴⁴ Exclusive approval rights to market a new drug or new medical device are very valuable to the pioneering company. The expensive and demanding processes for FDA approval carry with them a statutory form of limited time protection against competitor products. The protection from disclosure is assured by statutes and by FDA regulations that temporarily restrain the competitor's product from receiving approval during the period of exclusivity.

E. Effects of Failure in Clinical Tests

Experimentation by its nature involves trial and error. Some drugs and devices will harm some patients in the process of perfecting the product. Society, however, benefits from the learning that comes with experimental failure, modification and replication. For example, although individual elders may sustain injuries from a device as a result of their participation in the experimental implantation of that device, society benefits when the next version of the device is improved, thereby moving closer to a more durable and useful device for others' future use.

Society views this form of failed medical research as an acceptable risk, while the tort and regulatory systems deal with these individual

42. The most egregious cases have involved a failure to disclose to patients that they had been subjected to a medical experiment. *See* *Burton v. Brooklyn Doctors Hosp.*, 452 N.Y.S.2d 875 (App. Div. 1982).

43. *See* 21 C.F.R. § 812.30 (1999).

44. *See* 21 U.S.C.A. § 355(j)(5)(D) (West 1999) (providing a ten year prohibition on new drug applications based on information from previously filed applications).

failure consequences in distinctly different manners. Tort law seeks to deter errors of commission, such as the negligence of the aggressive surgeon trying a novel orthopedic technique.⁴⁵ By contrast, the separate system of federal regulation creates safeguards⁴⁶ and then oversees a periodic inspection of testing facilities, looking for errors of omission. Both of the two protective mechanisms have significant shortcomings from the viewpoint of optimizing elderly patient protection. The issue for elders is one of acceptability of risk within a set of protective mechanisms. That is, when the system fails, the elder may die or suffer significant health consequences that properly conducted research may have avoided. No one would assert that all research that carries risk must stop. This Article argues that the safeguards that are most important to elders, such as clarity of informed consent about risks, need to be upgraded as the number of elderly persons exposed to medical research experiments increases.⁴⁷

III. INVOLVEMENT OF THE ELDERLY IN MEDICAL EXPERIMENTATION

A. *Elders in Clinical Trials Are the Exception*

Whenever possible, most human clinical studies are done in younger adult populations. Researchers ideally want to avoid using persons with complicating factors that predispose the patient to illness or harm. Ethical issues arise when less-healthy individuals are asked to take a drug of unknown safety, because the drug may negatively affect their already-impaired health.⁴⁸ Elderly persons are infrequently used for clinical studies of drugs and devices in conventional product research testing because of complicating factors such as individual frailty⁴⁹ or the risk that unforeseen complications would cast a shadow of doubt over the developing product. As geriatric scholars have observed, “[c]linical

45. Both the surgeon and the hospital may be sued; the surgeon may be liable for use of a device not approved by the FDA. *See* *Staudt v. Froedtert Mem'l Lutheran Hosp.*, 580 N.W.2d 361, 363 (Wis. App. 1998) (holding a surgeon, but not the hospital, liable for use of an FDA approved device in a manner not approved by the FDA).

46. *See, e.g.*, 21 C.F.R. §§ 50.20 (1999) (FDA informed consent), 56.103 (1999) (IRB requirement), 312.50 (1999) (new drug sponsor duties), 812.100 (1999) (duties when using investigative medical device), 812.30 (1999) (FDA regulations regarding protecting human subjects); 45 C.F.R. § 46 (1998) (NIH regulations regarding protecting human subjects).

47. *See infra* Part IX (advocating the use of plain language in informed consent forms).

48. *See* HELENE LIPTON & PHILIP LEE, *DRUGS AND THE ELDERLY* 122 (1988).

49. *See* Specific Requirements on Content and Format of Labeling for Human Prescription Drugs, 62 Fed. Reg. 45,313 (1997) (acknowledging that impaired excretion of drugs, prior medical condition, and interactions with other medications were significant problems for elderly persons using pharmaceuticals).

trials attempt to avoid the confounding of study results because of the presence of other diseases, other drugs, and the inclusion of persons who have greater potential for developing new illnesses."⁵⁰

Statistics suggest that elderly Americans comprise twelve percent of the United States population and are the consumers of twenty-five percent of all prescription medications.⁵¹ According to federal statistics, thirty-eight percent of patients discharged from short-stay hospitals in 1996 were age sixty-five or older.⁵² Furthermore, of all surgical procedures performed in the United States in 1996, 35.77% were conducted on the elderly.⁵³ Despite these statistics, the federal regulatory system does not identify elderly persons as a class meriting special clinical research safety protections. Federal agency regulations specifically provide protected status for clinical trial subjects who are children,⁵⁴ prisoners,⁵⁵ pregnant women,⁵⁶ "handicapped, or mentally disabled"⁵⁷ and "economically or educationally disadvantaged,"⁵⁸ but not the elderly. Under the Department of Health and Human Services regulations, adults of all ages are subject to a generic set of rules;⁵⁹ however, pregnant women and their fetuses, prisoners and children are subject to separate sets of special rules.⁶⁰ When the National Bioethics Advisory Commission issued its report in December, 1998, it recommended that special attention be paid to evaluating the capacity of persons with impaired judgment, as well as those in various stages of mental illness.⁶¹ Although some elders suffer from mental illness or impaired judgment, no provision yet exists for the protection of all elderly patients.

50. LIPTON & LEE, *supra* note 48, at 122.

51. See Norma J. Owens et al., *Improving Compliance in the Older Patient*, in PATIENT COMPLIANCE IN MEDICAL PRACTICE AND CLINICAL TRIALS 107, 108 (Joyce A. Cramer & Bert Spilker eds., 1991).

52. See EDMUND J. GRAVES & MARIA F. OWINGS, CENTERS FOR DISEASE CONTROL AND PREVENTION, 1996 SUMMARY: NATIONAL HOSPITAL DISCHARGE SURVEY, in ADVANCE DATA NO. 301, at 1, 3 (1998).

53. See *id.* at 8.

54. See 45 C.F.R. § 46.401-.409 (1998).

55. See *id.* § 46.301-.306.

56. See *id.* § 46.201-.211. The fetus also has protected status under the federal regulations. See *id.*

57. 21 C.F.R. § 56.111(b) (1999).

58. *Id.*

59. See 45 C.F.R. § 46.101-.124 (1998).

60. See *id.* §§ 46.201-.211 (relating to pregnant women and their fetuses), 46.301-.306 (relating to prisoners), 46.405-.409 (relating to children as test subjects).

61. See NBAC, *supra* note 13, at 57-59.

In contrast to the general policy against using the elderly for experimentation, elderly patients have been enrolled as test subjects for those illnesses that occur with particular frequency in the elderly. In the case of surgical operations and medical device implantation, elderly patients may in fact be the best models for the research, if the nature of the underlying condition to be addressed is most often found among elderly persons.⁶²

B. FDA Trends

Recent FDA policy changes regarding drug testing in the elderly are likely to induce significantly greater use of elderly persons in pharmaceutical testing to evaluate new drugs and medical devices.⁶³ The FDA expects that manufacturers of drugs will now begin to study how their products are likely to affect older adults and to provide cautionary information aimed at the protection of elders as a result of the FDA policy changes.⁶⁴ The 1999-2000 implementation of this 1997 FDA policy⁶⁵ encourages manufacturers to do more testing with elders so that a set of dosing rules or cautions may be added to the labeling of over-the-counter or prescription drugs.⁶⁶

C. Availability of the Elderly for Testing

As a group, elders are the most frequent users of drugs and medical devices.⁶⁷ Elders are more likely to receive prescription drugs,⁶⁸ to have implant surgery, and to use assistive devices, like wheelchairs. Not coincidentally, elders may be more attentive to news of medical progress than are other adults. Elders may also have some of the greatest individual expectations of benefits from supporting and encouraging medical experiments. For example, a seventy-year-old female with arthritis pain may join a test of a pain medication more

62. Deteriorated physiological systems like the hips, for example, may be replaced with medical devices approved by the FDA. See 21 C.F.R. § 888.3360 (1999).

63. See FDA Draft Guidance for Industry on Content and Format for Geriatric Labeling, 64 Fed. Reg. 3302 (1999) (summarizing FDA regulations and providing guidance relating to label requirements).

64. See *id.*

65. See 21 C.F.R. § 201.57(f)(10) (1999).

66. The elderly purchase approximately "30% of all prescription drugs and 40% of all over-the-counter drugs." Rebecca D. Williams, *Medications and Older Adults*, 31 FDA CONSUMER, Sept.-Oct. 1997, at 15, 16.

67. See *supra* notes 51-53 and accompanying text (citing statistics regarding the elderly's use of drugs and medical devices).

68. See Owens et al., *supra* note 51, at 108 (providing an extensive discussion of the adverse drug reactions of elders utilizing multiple medications).

readily than a thirty-year old with occasional backaches. The elderly, as a group, may be the easiest adults to convince to participate in testing, especially when the elder trusts and/or requests advice of the health professional conducting the study concerning the illness to which the drug or device is directed.⁶⁹

Drug sponsors are now actively seeking out elders as test subjects to meet the FDA's 1997 change in policy.⁷⁰ Because the FDA now requires that manufacturers who sponsor a drug fully comprehend its effects on elders treated with the drug, it directed further testing of the new medication's potential effects on elders.⁷¹ One result of this further testing may be improved cautionary label statements or different dosage instructions for elderly persons.⁷²

With the expanded need for a generation of test results showing the effects in elders of existing and novel drug products, the drug research industry has looked to local, clinic-based physicians with large groups of ill patients.⁷³ This cost-driven dispersal of medical research to multiple sites negatively impacts quality control and full oversight of researchers' compliance with standards and safeguards. Some elders trust their physician so much that they will voluntarily enroll in a research project that carries significant risks.⁷⁴ An elder's special psychological reliance upon and trust in the good faith of his physician makes acceptance of the risk even more likely. Those who have studied the current state of informed consent note this dependent relationship⁷⁵ with concern, especially if the physician is being paid to bring more patients into the study group, because the ethical conflict of interest may pose significant problems in the long term.⁷⁶

69. See Eichenwald & Kolata, *supra* note 16, at A1 (discussing the elderly's trust for the health care worker's judgment).

70. See *supra* Part III.B (discussing FDA regulations and policy).

71. See 21 C.F.R. § 201.57(f)(10)(ii) (1999) (setting forth requirements for labels when the drug has been tested with and without elders).

72. The usual result of further clinical testing would be a modification of labeling to be cleared by the FDA as a supplemental new drug or device filing. See *id.* § 314.80 (requiring applicants for FDA approval to market new drugs to report adverse experiences in human subjects to the FDA).

73. See Eichenwald & Kolata, *supra* note 16, at A1.

74. See *id.* The existence of per-patient payments from the SMO to the physician may cloud the ethical issues regarding this trust relationship. See *id.*

75. See *id.*; see also Grant Bagley, *Informed Consent: The FDA's Perspective*, 48 FOOD & DRUG L.J. 181 (1993) (discussing the doctrine of informed consent with regard to women of reproductive years).

76. See Eichenwald & Kolata, *supra* note 16, at A1.

D. *Risks of Exploitation of Vulnerable Test Subjects*

The widely-observed vulnerability of elders to abuse in medical experimentation is a serious concern.⁷⁷ The elderly are particularly vulnerable to harm because of their diminished physical ability to tolerate the consequences of problems in surgery or problems with medication.⁷⁸ For example, a dosage error or an inappropriate combination of drugs has an exaggerated effect on a person with a pre-existing heart problem or hypertension, compared to a healthier, younger person.

Beyond physiology, the elderly may be vulnerable in the quality of their informed consent. The ability of ill subjects to understand and follow the meaning of a document⁷⁹ may be impaired, especially among those elders using psychoactive drugs.

Finally, elders may have either weak or no economic bargaining power. Incentive structures changed during the 1990s to increase the economic pressure on practicing physicians to enroll their patients into drug and device clinical studies.⁸⁰ Where elderly patients readily accept physician direction, and where elders more frequently visit clinics, greater numbers of elderly patients can be expected to voluntarily accept suggestions for their enrollment in a clinical testing protocol being conducted at their doctor's clinic.⁸¹ Moreover, Medicare health care payment structures impact the decisions of the elderly to participate in clinical studies. Specifically, these payment structures make the patient eager to have the opportunity for a cure free of charge, thereby reducing their interest in or ability to negotiate terms of participation in the "free" trial of a potentially beneficial new therapy.⁸²

77. See Williams, *supra* note 66, at 16.

78. For example, prior medical conditions, drug interactions and impaired kidney functions are among the problems the FDA has observed. See 21 C.F.R. § 201.57(f)(10) (1999).

79. See Evan G. DeRenzo et al., *Assessment of Capacity to Give Consent to Research Participation: State-of-the-Art and Beyond*, 1 J. HEALTHCARE L. & POL'Y 66, 69-70, 77-79 (1998); see also Michael S. Wogalter et al., *On the Adequacy of Legal Documents: Factors That Influence Informed Consent*, 42 ERGONOMICS 593 (1999) (analyzing studies of healthy subjects' understanding of consent documents).

80. See Eichenwald & Kolata, *supra* note 16, at A1.

81. An elder's financial problems in paying the clinic for normal, non-experimental treatments exacerbates the ethical problem. In fact, some ethicists feared that "vulnerable patients were being coerced through the lure of medical care to put their bodies on the line." Kurt Eichenwald & Gina Kolata, *For the Uninsured, Drug Trials Are Health Care*, N.Y. TIMES, June 22, 1999, at A1.

82. Specifically, these payment structures constrain the patient who wants to see a specialist. By joining a clinical study, however, the patient gets the "free" use of a potentially beneficial new therapy. See Eichenwald & Kolata, *supra* note 81, at A1 (noting that HMO patients are seeking out trials to avoid gate-keepers to see specialists).

IV. OVERSIGHT OF UNITED STATES MEDICAL EXPERIMENTATION

Medical experiments are overseen on at least four levels, and sometimes five: the physician; the IRB; the hospital; the FDA; and, where grants are involved in the research, the NIH. At the first level, the principal investigating physician has primary accountability for the safety of the participating patients.⁸³ Though day-to-day patient interaction on drug clinical trials usually involves the nurse or paraprofessional, higher intrusion drug trials with serious side effects are likely to be physician-supervised. Furthermore, surgical experimentation is always handled by specialized surgeons.

IRBs, the next level of oversight of medical experimentation and research to protect human subjects, have been in place for decades at the most sophisticated research institutions.⁸⁴ The IRB is established by regulation of the FDA,⁸⁵ the Department of Health and Human Services,⁸⁶ and other organizations, and usually consists of a group of hospital personnel and lay community volunteers. The concept of an IRB predates the FDA's regulatory involvement by many years⁸⁷ and statutory requirements for IRB use in NIH research date back to 1974.⁸⁸ IRB members recognize their own importance "because research investigators have an inherent conflict of interest."⁸⁹ IRB operations are the primary focus of recommendations from government panels for increasing efforts to protect patients,⁹⁰ although the flaws of IRBs have been widely discussed⁹¹ and many medical journals do not appear to require IRB approval of studies.⁹²

83. This comes with the physician-patient relationship and is enforced by malpractice tort actions.

84. See NBAC, *supra* note 13, at 17.

85. See 21 C.F.R. § 56.101 (1999).

86. See 45 C.F.R. § 46.103 (1998).

87. See NBAC, *supra* note 13, at 17.

88. See National Research Act, Pub. L. No. 93-348, 88 Stat. 342, 352 (1974) (codified as amended in scattered sections of 42 U.S.C.) (noting the requirement of involving review boards in human clinical trials of drugs performed at, or for, the National Institutes of Health).

89. Alison Wichman, *Protecting Vulnerable Research Subjects: Practical Realities of Institutional Review Board Review and Approval*, 1 J. HEALTHCARE L. & POL'Y 88, 92 (1998).

90. See NBAC, *supra* note 13, at 65.

91. See OFFICE OF INSPECTOR GENERAL, U.S. DEPT. OF HEALTH AND HUMAN SERVICES, INSTITUTIONAL REVIEW BOARDS: A TIME FOR REFORM, NO. OEI-01-97-00193 (1998) [hereinafter OIG REPORT, A TIME FOR REFORM]. The report can be found at <<http://www.hhs.gov/progorg/oei/search.html>> under search term "institutional review boards" (providing extensive analysis of the weak points in the current IRB system). The Office of Inspector General examined the records of the IRBs, conducted interviews at a selected set of institutions, and drafted suggested changes to the current IRB mechanisms. See *id.*

92. See Amdur & Biddle, *supra* note 31, at 909.

The IRB's paper-intensive task is to review the protocols and methods of each clinical study involving a particular institution to ensure that the risks of the experiment are reasonable in light of the protective measures and benefits of the study.⁹³ The IRB also receives and reviews copies of the informed consent documents.⁹⁴ Members of the IRB may ask questions of the investigating physician, or may delegate the review of protocols to the chair of the board, who is usually a senior physician.⁹⁵ IRB leaders have complained that reports of adverse patient effects constitute an "avalanche" of documents⁹⁶ which overwhelms the resources assigned or volunteered for the IRB.⁹⁷ A study of the "thankless job" of IRB reviewers called on sponsors of research to provide more support of reviews.⁹⁸ Indeed, workload increases and shortages of funds and staff have become critical problems for IRBs.⁹⁹ Therefore, although this patient protection system is in place, its effective operation is subject to the many strains and stresses of the modern health care environment.

IRBs are silent overseers who operate in the paper-laden netherworld of research institutions. The patient never sees the behind-the-scenes work of the IRB, and the relatively infrequent audits of IRBs are loosely communicated to other such groups. Accordingly, IRBs may be the least visible method of protecting patients against harm from experimental drugs or medical devices. Under FDA rules, some IRBs review research from outside their institution, some companies maintain their own IRB, and some IRBs exist independent of any institution, operating instead by contract as a service provider to any study management organization or individual physician-investigator who wishes to use their services.¹⁰⁰ Regulations do not require any direct connection between the research institution and the IRB itself.¹⁰¹

93. See OIG REPORT, PROMISING APPROACHES, *supra* note 1, at 3.

94. See 21 C.F.R. § 56.111(a)(5) (1999); OIG REPORT, PROMISING APPROACHES, *supra* note 1, at 3.

95. See 45 C.F.R. § 46.110 (1998) (setting forth expedited review procedures).

96. See Bruce Gordon & Ernest Prentice, *Selective Review of External Adverse Events: One IRB's Response to the Avalanche of IND Safety Reports*, IRB: A REV. HUM. SUBJECTS RES., May-June 1999, at 10.

97. See *id.*

98. See Jonathan Moreno et al., *Updating Protections for Human Subjects Involved in Research*, 280 JAMA 1951, 1956 (1998).

99. See OIG REPORT, PROMISING APPROACHES, *supra* note 1, at 1.

100. See 21 C.F.R. § 56.107 (1999) (setting forth requirements for IRB membership).

101. See *id.* § 56.102(g). In addition, each regulated institution "designates" boards for the task, but the boards may be separate from the institution. See *id.*

An injury or death occurring during a clinical test may never come to the attention of the IRB that authorized the study. Although the IRB has a duty to monitor studies after approval has occurred, a federal commission has observed that relatively few IRBs actively involve themselves in monitoring completed studies.¹⁰² The voluntary membership and part-time efforts of institution employees who participate on the boards do not actually equip IRBs to function as proactive examiners of how well the clinical physicians carry out promises of patient protection.¹⁰³ Over a ten year period, adverse event reports received at one IRB quadrupled, vividly demonstrating how resource shortfalls may influence the effectiveness of board members.¹⁰⁴

Recent litigation has challenged the institutional peer review process for research misconduct, attacking the peer participant physicians for libel or economic tort. This development raises new barriers to institutional self-policing because when an allegation of fraud or abuse is made, the targeted physician might sue the members of the reviewing committee in addition to the institution itself.¹⁰⁵

The remaining overseers of the safety of clinical research are outside the institution. These overseers, such as the grant-paying government agency, sponsoring foundation or sponsoring manufacturer of a drug or device who pay for the study's costs, have direct financial interests. These sponsors want to ensure that data will be accurately recorded and reported in order to achieve product approval.¹⁰⁶ For NIH studies, the external quality examiners have included audit teams from the NIH Office for Protection from Research Risks.¹⁰⁷ These teams protect the NIH's interest in getting value for its grant money.¹⁰⁸ External quality examiners for the FDA include the individual FDA field investigators who question employees and review practices of research institutions at

102. See NBAC, *supra* note 13, at 71.

103. See Wichman, *supra* note 89, at 88.

104. See OIG REPORT, PROMISING APPROACHES, *supra* note 1, at 4.

105. See *Angelides v. Baylor College of Med.*, 117 F.3d 833 (5th Cir. 1997). Alternatively, the institution that poses the challenge to misconduct may itself be accused of having committed fraud. See, e.g., *United States ex rel. Berge v. Board of Trustees of Univ. of Ala.*, 104 F.3d 1453 (4th Cir. 1997) (illustrating a case where the university was charged with fraud pursuant to the False Claims Act).

106. See 21 C.F.R. § 314.125(b)(14) (1999).

107. This office was recently made a part of the Health and Human Services Department's Office of Public Health and Science. See *infra* notes 157-60 and accompanying text (explaining that this change is expected to result in greater efficiency as an oversight body).

108. See *Protecting Research Subjects*, HHS FACT SHEET (U.S. Dept. of Health and Human Services) Nov. 4, 1999, at 1 [hereinafter HHS FACT SHEET].

the direction of FDA headquarters managers.¹⁰⁹ Each federal agency has its own mechanism to adjudicate clinical investigator misconduct,¹¹⁰ the result of which may lead to a prohibition on future medical research by the accused physician.¹¹¹ Each agency also has the ability to halt work on drug research by an institution, as the NIH did in 1999 with the University of Illinois at Chicago¹¹² and Duke University.¹¹³ The repercussions of embarrassment and cost would be a real deterrent if enforcement occurred more frequently and was more efficient than the slow process now in place.¹¹⁴

V. ADVERSE HEALTH EFFECTS ON TEST SUBJECTS

Many tests on drugs and devices succeed and the products are helpful. Inevitably, however, experiments in health promotion or protection sometimes fail. Failure may be either a statistically disproven hypothesis or a direct harmful consequence to tested individuals. Of those that do not succeed, a very small portion of patients who experienced a bad outcome may complain to regulators or sue the researcher. A "bad" outcome may be the death, incapacitation or illness of the person who was involved in the clinical test at a rate more frequent or with a consequence more severe than is found in the average population. Overdose, drug interaction,¹¹⁵ and physiological stresses from surgery or medication are among the risks involved in medical testing of the elderly. The fact that approximately eighty-six percent of persons over age sixty-five use at least one long-term medication makes testing of new medications on this group more challenging.¹¹⁶ No published statistics on adverse consequences in

109. Procedures of the FDA field investigators are readily viewed on the Internet at <<http://www.fda.gov>> and those of the NIH at <<http://www.nih.gov/grants/oprr>>.

110. The FDA uses "disqualification" after a hearing on the allegations. See 21 C.F.R. § 312.70 (1999).

111. See Debra Parrish, *Improving the Scientific Misconduct Hearing Process*, 277 JAMA 1315, 1316 (1997) (setting forth relevant information regarding the NIH trials); see also Bagley, *supra* note 75, at 182-84 (discussing the FDA trials).

112. See Brainard, *supra* note 26, at A44.

113. See Charo, *supra* note 15, at A64.

114. For example, if audits resulted in cutting off funds, career damage to those who withheld funds from research protection and IRB roles might have deterred other administrators. See Jeffrey Brainard, *U. of Illinois at Chicago Chancellor Resigns Following Research Shutdown* (visited Sept. 13, 1999) <<http://www.chronicle.com/daily>>.

115. See J. P. GRIFFIN ET AL., *A MANUAL OF ADVERSE DRUG INTERACTIONS* 62 (4th ed. 1988) (noting how diminished kidney function makes drug interaction a serious problem).

116. See PHILIP LEY, *COMMUNICATING WITH PATIENTS* 63 (1988); see also Owens et al., *supra* note 51, at 108-09 (demonstrating the increased risk of adverse drug reactions in older patients).

medical experiments offer a reliable measurement of this safety concern.

For purposes of this Article, a medical research experiment on an elderly patient will be considered “bad” if injury, illness, worsening of the physical condition or death of the person occur as a consequence of the experiment. No data exists on the total number of patients involved in clinical studies or the number of those at risk. Yet, as one study concluded, “there have been a sufficient number of cases of dubious research practices with vulnerable populations to raise concern about the adequacy of the existing regulations.”¹¹⁷

In a typical hypothetical case, an institution or a study management organization contracts with a sponsoring company to test a new drug or device. An elderly person, during a visit to a physician or clinic, is urged to sign a consent form to participate in a placebo-controlled drug trial to allow for the adaptation of a new device to be used during a previously scheduled surgical procedure. The person signs the consent form, the drug or device is administered, and an unexpected injury or death occurs. Typically, the research continues—the experiment would be halted only if the rate of adverse effects is too frequent or the adverse effects themselves are too severe.

No one has published statistics on how frequently these dangers or illnesses result from flawed work by researchers such as incorrect doses of medication or errors in experimental surgery. Ironically, the absence of universally reliable statistical data about incidences of harm makes the issue unlikely to be accepted for publication in a scientific journal. This Article, however, relates to remedies and societal policy choices. The absence of a firm statistical data set does not preclude legal analysis in the context of harm to elder patients.

VI. REGULATORY RESPONSES TO ADVERSE EXPERIMENTAL EFFECTS

When medical research results in a serious adverse event or death, several responses are possible. From the physician-investigator’s viewpoint, death may have been the anticipated result of the illness being studied (e.g., a terminally ill brain tumor patient who underwent experimental surgery with an acknowledged low chance of tumor remission). Alternatively, the adverse event may be a novel data point that teaches surgeons not to use the device in that organ of the body. Self-reporting of errors and flaws in following research protocol is unlikely to occur unless the physician or surgeon is required to

117. Moreno et al., *supra* note 98, at 1951.

announce the error. If it exists, such a requirement will arise through the institution's rules that the physician-investigator file a report with the risk manager of the hospital and the IRB. The hospital's risk management group will also be involved in the review because there are potential liability and insurance issues.

The IRB's oversight role, when exercised, can be an important part of the hospital's response to death or serious injury. But adverse reaction reports have proliferated,¹¹⁸ causing many IRBs to approve the testing protocol without adequately using their authority to follow up on the research as it progresses.¹¹⁹ The FDA has expressed concern about IRBs' level of attention to the safety issues in medical device studies, but the FDA cannot inspect as many IRBs in as much depth as would be necessary to assure their quality.¹²⁰

If a death or serious injury occurred during an FDA-reviewed study, the terms of the application for FDA permission to commence drug or device studies would require that a report be filed with the FDA drug or device review group that had cleared the study.¹²¹ In addition, a requirement to notify by phone or e-mail the FDA's Medwatch program for physician reporting of drug-related injuries may also be triggered by the injury.¹²² If the grant for the research came from the NIH, it would also expect a report when one of the patients in a study it sponsored suffered a serious adverse effect.¹²³

It is unlikely that either the NIH or the FDA will ever be involved in a privately-funded surgeon's research with new methods, or informal studies of a custom device¹²⁴ or an existing marketed drug. If the surgeon's research is privately funded, the product sponsor need not have made a submission for government approval of the product; and if the hazardous medical device that caused the injury is not pursued to later marketing application stages, neither the NIH nor the FDA will ever see the data. If, however, the product is later submitted for FDA approval, then all research studies must be submitted to the agency,

118. See OIG REPORT, PROMISING APPROACHES, *supra* note 1, at 4.

119. See OIG REPORT, A TIME FOR REFORM, *supra* note 91, at 6.

120. See Joanne R. Less et al., *Institutional Review Boards and Medical Devices*, 272 JAMA 968, 968 (1994).

121. See 21 C.F.R. § 812.46(c) (1999). Implicit in this provision is an obligation to communicate to the FDA as a prerequisite for doing further research. See *id.*

122. Former Commissioner David Kessler created this program to centralize the FDA's adverse effect reporting systems. See *id.* § 314.80(f).

123. See 45 C.F.R. § 46.103(b)(5) (1998).

124. See 21 U.S.C. § 360j(b) (1994).

including those that showed problems.¹²⁵ The concealment of adverse data from the FDA concerning a drug approval application is a felony.¹²⁶

By contrast, silence about injuries in non-regulated human testing is legal under current law. Moreover, if the documentation of the adverse event exists within the institution's files, it is not considered a "coverup." Nevertheless, this illustrates that federal regulation is not a panacea—government control does not reach all medical research in which elderly persons might be at some risk of adverse health effects.

The current system of federal regulatory oversight of medical research has been criticized and groups inside the government and an outside commission have urged changes.¹²⁷ Suggested improvements usually focus on tightening the regulatory constraints placed on large hospital-based clinical study groups. The vehicle of choice for this sophisticated control is the IRB.¹²⁸ Such a solution, however, would only moderately aid elders, because an estimated seventy-five percent of research is done for the drug industry.¹²⁹ The disdain of some members of the research community for the large amount of for-profit medical research performed on patients is evident in the 1998 report of the National Bioethics Advisory Commission ("NBAC").¹³⁰ This blue ribbon expert panel focused on fixing the models used in large, grant-seeking institutions and ignored the problems in unregulated industry research. The NBAC's attitude, however, will not change the reality that elderly patients are more likely to be sought by drug and medical device researchers outside of academic institutions. Additionally, patients like these may never hear of the IRB, much less understand its function.

The institutional-elite model of IRB review of large university-based clinical trials is slipping out of prominence in American clinical research, with changes occurring in several directions simultaneously. First, the local review board members are overworked and

125. See 21 C.F.R. § 314.125(b)(14) (1999) (refusing to approve an application that does not include adequate evaluative information about the drug).

126. See 1 O'REILLY, *supra* note 32, § 8.

127. See NBAC, *supra* note 13, at 87; OIG REPORT, A TIME FOR REFORM, *supra* note 91, at 6.

128. This volunteer panel within an institution has the legal responsibility to evaluate patient safety issues in drug and medical device experiments at that facility. See 21 C.F.R. § 56.109 (1999) (regarding the FDA); 45 C.F.R. § 46.109 (1998) (regarding the NIH).

129. See OIG REPORT, PROMISING APPROACHES, *supra* note 1, at A-1 n.3.

130. See NBAC, *supra* note 13, at 87 (providing the statement of Alexander Capron).

underfunded,¹³¹ reducing the qualitative scrutiny that individual tests receive while the government considers loading additional duties on top of their existing paperwork.¹³² IRBs at hospitals are likely to suffer from the modern stresses on all hospitals to cut costs, focus on financial consequences of the hospital's activities, and streamline processes.¹³³ IRB review was meant to be a prerequisite for publication of medical research; yet, a study found that independent researchers may gain publication in numerous journals even without IRB review.¹³⁴

The second area of change is in the large volume of medical research that is performed outside of academic centers, constituting perhaps half of all clinical studies underway today.¹³⁵ This means that the presumptive mechanism of institutional control that had existed in academic centers will be irrelevant to the actual tests run on thousands of research participants. The landscape of medical research, once dominated by government grants to large institutions for expensive research efforts, has changed in response to market forces. As more study management organizations perform greater percentages of clinical testing for pharmaceutical and medical device companies, there will be proportionately fewer classic university-based, high cost venues conducting large volumes of drug and device testing. The result may be an eventual dual tier of testing. The first tier is the government and foundation grant money paid to large institutions for research with high overhead costs but high patient protection levels. The second tier is medical product-specific testing funds spent through study management organizations in thousands of dispersed clinics and medical care venues delivering lower-cost research results by cutting overhead.

The cost gap in such a two-tier future has both safety and patient protection consequences.¹³⁶ The elite medical research institutions may be subjected to more costly measures, while the total funds available for nonprofit and governmental support of medical research are constrained by budget considerations. Medical care for an elderly person who receives a new arthritis drug, a new form of colostomy, or a new hip joint costs less to the product's sponsor when the patient is processed

131. *See id.* at 71; *see supra* Part IV (discussing oversight of U.S. medical experimentation).

132. *See* OIG REPORT, PROMISING APPROACHES, *supra* note 1, at 6.

133. *See id.* at 1 (noting that "[m]anaged care, with its emphasis on cost control, is squeezing research support at academic health centers and limiting providers' time for administrative duties such as IRB participation").

134. *See* Amdur & Biddle, *supra* note 31, at 909.

135. In the absence of a central statistical reporting site, this author credits the FDA estimate that about half of clinical studies are now being performed outside of institutions.

136. *See* Charo, *supra* note 15, at A64.

through lower-cost individual physicians or smaller clinics. In this context, a patient's protection is still subject to the moral and ethical practices of the individual physician, but institutional controls fade in their ability to influence patient protections.

VII. THE ROLE OF THE REGULATORY SYSTEM IN PROTECTING ELDERS IN RESEARCH

Regulatory agency response to harm from an adverse experimental event varies by agency. One model, exemplified by the FDA, is that of the "gatekeeping regulator," for whom accuracy of the drug or device experiment's statistical result is crucial to a pre-market product approval decision.¹³⁷ The other model is that of the "funding agency overseer," which pays for research to be done and which requires the testing to conform to government-imposed patient protection criteria.¹³⁸ This is the role of the NIH and other grant-awarding agencies that dispense money to applicants in support of their pursuit of knowledge.¹³⁹

A. *The Role of Regulators*

The FDA operates within the context of an institutionalized history of skepticism about claims of drug and device safety.¹⁴⁰ Studies funded by product sponsors under an FDA-reviewed test protocol and an FDA product "exemption," such as an investigational medical device exemption,¹⁴¹ are subject to significantly more intense scrutiny than that which occurs with abstract basic research. This is because the product sponsor oversees the quality of the testing data before submitting it to the FDA, and the FDA carefully examines the sponsor's submissions before approving the product for sale. Vaccines,¹⁴² human drugs,¹⁴³ and human-use medical devices¹⁴⁴ may not be used on patients until the

137. See 21 C.F.R. § 314.125 (1999) (listing the reasons for the FDA's denial of drug approval, including inadequacy of controls on experimentation).

138. These criteria take the form of the NIH's assurances of compliance under 45 C.F.R. Part 46. See 45 C.F.R. § 46.111 (1998) (listing the criteria for IRB approval).

139. See *id.* § 46.103 (noting that the NIH ties research funding eligibility to assurances of compliance with patient protection rules).

140. See I O'REILLY, *supra* note 32, §§ 13, 18 (providing a review of FDA history relating to drug and device safety).

141. See 21 U.S.C. § 360j(g) (Supp. 1997).

142. The FDA regulates these under authority of the Public Health Service Act. See 42 U.S.C.A. § 262 (West 1999 & Supp. 1999).

143. See 21 U.S.C.A. § 355 (West 1999).

144. See 21 U.S.C. § 360j(g) (Supp. 1997).

FDA has granted an exemption from the statutory approval requirements, or unless an FDA exclusion applies. Therefore, the FDA grants "exemptions" from pre-market approval for the limited testing of a new drug or a new device. If a death or serious injury occurs during an FDA-sanctioned research study, it must be reported to the FDA immediately after the sponsoring organization learns of the tragic event.¹⁴⁵ Each adverse event report is entered into the FDA's tracking system. Adverse events are considered by the FDA medical review officers when the sponsor seeks approval of a subsequent exemption, or later at the stage of pre-marketing approval for the drug or device.¹⁴⁶

B. Oversight of NIH-Funded Studies

A structure for the protection of clinical research patients has existed under the National Institute of Health for many years. Institutions that receive NIH grants must provide a formal written "assurance" of compliance with NIH rules for informed consent, explanation of risks and other rights of test subjects.¹⁴⁷ Each institution must also maintain a structure in place to audit and to report to the NIH if there are flaws in patient protection within a particular study.¹⁴⁸ An institution wishing to receive future research funds will undertake to police its medical researchers. The NIH Office of Protection from Research Risks ("OPRR") may also audit a grant-funded facility.¹⁴⁹

Although the NIH is not in a command-and-control relationship with the physician-investigator as is the FDA, the regulations on informed consent and patient protection are part of the NIH's agreements with grant recipient institutions.¹⁵⁰ In addition, Congress requires IRB examination of research by NIH grantees.¹⁵¹ Non-compliance with the regulations by an IRB,¹⁵² hospital, or investigator would imperil future

145. See 21 C.F.R. § 312.32(c) (1999).

146. See *id.* § 314.80. This provision compels researchers to submit adverse event reports; the file is examined when another exemption is requested for further studies. Furthermore, if the drug sponsor fails to adequately and promptly report adverse reactions, the drug will be disapproved. See *id.* § 314.125(b)(14).

147. See 45 C.F.R. § 46.103 (1998).

148. See *id.* § 46.103(b)(5).

149. This entity's functioning is described in detailed charts on its website, available at <<http://www.nih.gov/grants/oprr>>.

150. See 45 C.F.R. § 46.103 (1998); see also *infra* note 265 (setting forth the regulations regarding informed consent).

151. See National Research Service Award Act, Pub. L. No. 93-348, 88 Stat. 342 (1974) (adding section 474 of the Public Health Service Act).

152. See Charles Marwick, *NIH Research Risks Office Reprimands Hospital Institutional Review Board*, 263 JAMA 2420, 2420 (1990).

federal grant funds. This powerful deterrent to laxity earns the attention of university managers and hospital executives. Thus, the NIH's extensive procedural norms¹⁵³ are enforceable by threat to the institution's future funding or, in the case of fraud, by referral for prosecution.¹⁵⁴ Scientific misconduct is a serious legal issue for medical institutions.¹⁵⁵ Adverse effects of medical testing on experiment subjects in an NIH-funded study may be evaluated by the NIH official responsible for the grant.¹⁵⁶ Thus, the role of a grant-dispensing entity includes the responsibility to make sure that the research is properly conducted and complies with patient protection regulations.

NIH oversight focuses more on fraud than on conditions of patient consent and patient voluntariness,¹⁵⁷ but the OPRR does audit clinical documentation, and in some cases has penalized institutions whose research did not adequately protect patients.¹⁵⁸ The conflicting missions of promoting and policing research have produced internal controversy within the federal government. The OPRR was moved out of NIH in 1999 as part of a reorganization¹⁵⁹ and is expected to operate more effectively as an oversight body located within the parent organization of NIH, the health component of the federal Department of Health and Human Services.¹⁶⁰

Detection of fraudulent data such as falsified reports on phantom patients has been a goal of the NIH; however, the NIH's focus is more

153. See 45 C.F.R. § 46 (1998) (providing NIH requirements for the protection of human subjects).

154. NIH-funded studies rarely result in fraud litigation, but the potential for large scale financial problems is a matter of concern for all NIH-grantee institutions. See, e.g., *United States ex rel. Berge v. Board of Trustees of the Univ. of Ala.*, 104 F.3d 1453, 1462 (4th Cir. 1997) (reversing a judgment against university officials for falsifying information in NIH grant applications for lack of materiality).

155. See generally Debra Parrish, *Scientific Misconduct and the Plagiarism Cases*, 21 J.C. & U.L. 517 (1994) (providing a useful analysis by a former counsel to the NIH).

156. The NIH procedures are addressed with charts. See <<http://www.nih.gov>>.

157. See Paulette Walker Campbell, *Head of NIH Seeks to Move Unit That Oversees Research with Human Subjects*, CHRON. HIGHER EDUC., June 11, 1999, at A36.

158. See 45 C.F.R. § 46.123 (1998) (providing authority for NIH to terminate or suspend support for research if the institute does not comply with prescribed safeguards).

159. See HHS FACT SHEET, *supra* note 108, at 1. The background for this fact sheet is found in the Report to the Advisory Committee to the Director, NIH from the Office for Protection from Research Risks Review Panel dated June 3, 1999. See <<http://www.nih.gov/grants/oprr/references/060399b.html>>.

160. The move came after a study reported a need for more resources and more independence. In particular, "[s]ome observers have feared that the office has cared more about protecting NIH research than protecting human subjects." Campbell, *supra* note 157, at A36.

on “data integrity” than on the protection of patients.¹⁶¹ The progress of NIH’s advanced cutting-edge research work is important to medical science, and the integrity of data is an important societal value. NIH’s response to the 1999 National Bioethics Advisory Commission report included suggestions to re-emphasize patient protections and informed consent in NIH studies.¹⁶²

C. *Motives of the Product Regulators*

A grant-paying agency such as the NIH has a set of implicit motives different from those of a product-approving agency when responding to a report that an elderly patient in a research study has died as a result of such research. NIH generally acts as a funder and not as a police inspector; by the time of the report, its grant money has been spent. NIH requires adherence to criteria for patient protection because NIH decided that the test should receive federal funding, and its interests are affected when unanticipated harms flow from that funding decision. Arguably, the NIH decision in favor of funding the experiment contributed to the occurrence of the detrimental event.

By contrast, drug and device companies are more willing to accept some adverse effects as a reasonable part of medical research.¹⁶³ The FDA officials who review these clinical study results serve a policing role on private, for-profit data gathering. The FDA’s motive is safeguarding patients against the potential that the privately funded studies could cause harm to patients. Thus, the motives of the NIH and the FDA in oversight of research safety are not identical,¹⁶⁴ although the federal agency criteria for patient protection have been elucidated in a “common rule.”¹⁶⁵ The FDA neither determines who may do what

161. See NIH website, <<http://www.nih.gov/grants/oprr>>.

162. See NBAC, *supra* note 13, at 4 (recommending informed consent procedures that establish that when capable, a research subject may consent without involvement of a third party and recommending increased safeguards for subjects who may not be able to give informed consent due to the complexity of the research or their own capacity).

163. Presumably, planners of private clinical study costs will include a financial reserve to pay claims that may arise from injuries to clinical test subjects. By contrast, the NIH and the FDA are exempt from most claims in tort because of the discretionary function exemption to the Federal Torts Claims Act. See 28 U.S.C. § 2680(h) (1994).

164. Though the agencies interact and have the same agency head at the Cabinet level, they are not the same entity in legal or operational terms. See *United States ex rel. Zissler v. Regents of the Univ. of Minn.*, 992 F. Supp. 1097, 1103-04 (D. Minn. 1998), *rev’d*, 154 F.3d 870 (8th Cir. 1998) (demonstrating independent knowledge of the NIH and the FDA of profits the university derived from research drug and the difference to each agency’s function in grant investigations).

165. See Federal Policy for the Protection of Human Subjects, 56 Fed. Reg. 28,003, 28,004 (1991) (to be codified at 7 C.F.R. § 1c, 10 C.F.R. § 745, 14 C.F.R. § 1230, 15 C.F.R. § 27, 16 C.F.R. § 1028, 22 C.F.R. § 225, 24 C.F.R. § 60, 28 C.F.R. § 46, 32 C.F.R. § 219, 34 C.F.R. § 97,

research, nor who pays for it, as the NIH does. Therefore, the FDA's relationship with the physician-investigator is more analogous to that of a stern policeman than a dismayed benefactor.

Viewed another way, serious harm to patients in a regulated entity's drug or device experiment has informational aspects. Patient harm during a clinical trial does not implicate an FDA choice in the same way that a similar harm in NIH-funded trials reflects upon NIH because the FDA did not "choose" to have a particular test done. The FDA knows that other applicants will apply to the FDA after the first experiment has failed, seeking permission to run a similar test at their own expense.

NIH has a strong incentive to share experimental data to avoid repetitive failures. By contrast, the FDA staff members cannot lawfully divulge the contents of the failed applicant's submission to subsequent researchers¹⁶⁶ because the drug testing submissions constitute trade secrets or commercially sensitive data of the company that invested in their creation.¹⁶⁷ At best, the FDA staff can place the test on "clinical hold" while suggesting revisions to the methods and protocols being utilized.¹⁶⁸ In 1997, certain statutory amendments considerably curtailed the power of the FDA to place experiments on hold.¹⁶⁹ Congress did not, however, alter the secrecy provisions of drug and device testing laws through the 1997 amendments. Thus, the FDA is still prohibited from disclosing the protocol of a safety study by one company, thereby preventing its competitors from emulating or perfecting their subsequent inquiries.¹⁷⁰ This prohibition makes it clear

38 C.F.R. § 16, 40 C.F.R. § 26, 45 C.F.R. § 46, 45 C.F.R. § 690, 49 C.F.R. § 11). The common rule specifies that IRBs must determine that risks to subjects are minimal and reasonable, that selection of subjects is equitable, that informed consent is sought and documented, that data is protected and that any special safeguards for subjects are met. *See id.* at 28,015-16.

166. *See* 21 U.S.C. § 331(j) (1994) (establishing statutory provisions prohibiting the use or revelation of any method or process considered a trade secret).

167. *See* 21 C.F.R. § 314.430(c) (1999) (specifying that previously undisclosed data is not available for public disclosure).

168. The FDA can prevent sponsors from delivering the drug or device to the patients pending FDA agreement that the test is safe. *See* 21 C.F.R. §§ 312.42 (1999) (declaring that when a proposed or ongoing study "is placed on clinical hold," new subjects may not be recruited and patients already participating in the study may not receive the investigative drug); 812.30 (1999) (providing that the FDA may disapprove or withdraw any device where there is an unreasonable risk of harm to the subjects).

169. *See* Pub. L. No. 105-115, § 117, 111 Stat. 2315 (1997) (modifying 21 U.S.C. § 355(I)); *see also* 63 Fed. Reg. 68,676 (1998) (noting that FDA clinical hold orders were the subject of limitations on the FDA, compelling it to more readily allow investigations to proceed). A study may be placed on clinical hold if the subjects are exposed to an unreasonable risk of harm. The FDA must respond to any written request from the sponsor within 30 days. *See* Pub. L. No. 105-115, § 117, 111 Stat. 2315 (1997).

170. *See* 21 C.F.R. § 312.130 (1999).

that the FDA's statutory role is to block access to human patients if the test is deemed unsafe, not to improve upon the test by sharing methods and outcomes with competing drug and device makers.

D. How Clinical Data Is Utilized

The NIH uses the reports received from grantee research as part of its overall research plans in a particular disease area. A successful record of experimentation may earn more grants for that institution and researcher in the future. Because the NIH does not have a product-regulatory focus, the publication of the medical researcher's discoveries usually adds to the general community of knowledge. In some cases, however, the study results may be used for the future development of products.¹⁷¹

The FDA does not generally initiate clinical tests; it receives results of tests performed by others and acts as a gatekeeper, demanding sufficient proof of the effectiveness of the product before marketing can begin. The FDA has disseminated its guidance about testing methods¹⁷² and its regulations regarding informed consent to the sponsors of drugs, vaccines, medical devices and other products.¹⁷³ As a result, the FDA expects these sponsors to structure their studies in a manner that meets the FDA's needs and adheres to the requirements of the informed consent rules.

The grant of FDA permission to perform human clinical studies in support of a drug or medical device is known as an "investigational new drug exemption"¹⁷⁴ or an "investigational device exemption."¹⁷⁵ The FDA's granting of the exemptions is dependent on the sponsor's multi-volume submissions of documents showing the sponsor's ability to generate well-controlled scientific proof of safety and efficacy with statistically valid findings from human subject experimentation.¹⁷⁶ FDA oversight of human research protects against erroneous factual conclusions by the sponsor regarding the relative safety of the

171. This could take many forms, such as a vaccine developed with NIH funds and commercialized under a patent license agreement.

172. FDA clinical testing guidelines are not regulations and are flexible. See <<http://www.fda.gov/cder/regguide.html>> (detailing numerous testing guidelines).

173. See 21 C.F.R. § 50 (1999) (listing FDA regulations for Protection of Human Subjects).

174. *Id.* § 312 (listing FDA regulations for Investigational New Drug Applications).

175. See *id.* § 812 (listing FDA regulations for Investigational Device Exemptions).

176. The FDA will deny a product approval, or revoke an exemption allowing clinical tests, if the sponsor does not produce valid findings from adequate testing. See 21 C.F.R. §§ 312.20 (1999) (denial of application for new drug exemption), 812.30 (1999) (denial of application for medical device).

experiment. Its primary focus is the approval of a product. The FDA process measures the validity of the experiment as a statistical exercise from which the behavior of the medication or device in humans can be predicted. The key measurement is the replication of the experimental results, not the therapeutic benefit of the product to the individual drug recipient. For example, the FDA focused on placebo control studies for many years in order to obtain improved statistical purity of the results of a drug test.¹⁷⁷ This scrutiny is significant because a placebo model carries no benefit for the human subject in an experiment's "control" group.

There may be some misunderstanding among the public about the protections that the government provides. Patients who are in pre-approval drug or medical device studies and expect the government to monitor the ethics or scientific quality of their physicians' activities are misinformed regarding the government's role. In practice, only a small portion of the patient records in any particular drug study may be inspected, and even these inspections occur long after the clinical trial occurs. Indeed, the FDA engages in a retrospective paper review, not an ongoing collaborative effort between researcher and reviewer as may be true of a significant NIH project. Moreover, the overworked and underfunded IRB that is on the front line is subject to federal inspector criticisms only when and if an audit occurs.¹⁷⁸

The relatively recent appearance of SMOs has facilitated the production of clinical data in FDA-preferred computerized standard formats, reducing some of the costs for pioneer drug research companies.¹⁷⁹ Once the sponsor is satisfied with the data generated by the SMO from several clinical testing sites (e.g., a study of skin ulceration on immobile elders in six nursing homes), the sponsor submits a new drug application to the FDA and an FDA medical review officer will then determine whether sufficient data exists to show that the drug is safe and effective.¹⁸⁰ As part of the review of a new drug application, the FDA staff may decide to check the documentation of

177. The controversies over the measurement of drug effectiveness have been a frequent topic of legal as well as scientific controversy. The legal history is explained in depth in I O'REILLY, *supra* note 32, § 15.06.

178. See Moreno et al., *supra* note 98, at 1955-56.

179. The tests conducted for generic drugs are small, quick studies of healthy volunteers. Accordingly, this Article focuses on the pioneer developers' research where extensive human studies are required. See 21 C.F.R. § 314 (1999).

180. See 21 U.S.C. § 355 (1994) (prohibiting the introduction into commerce of a new drug without FDA approval); 21 C.F.R. § 314 (1999) (providing new drug approval standards).

the clinical trial and may direct field investigators to conduct an on-site inspection at one or more of the clinical sites.

Therefore, in clinical testing of drugs and devices, the FDA is a passive recipient of past data and auditing records of work completed months or sometimes years before FDA oversight. The review it conducts is a review of a cold paper trail. The FDA has no relationships with patients and does not instigate or fund drug research. Accordingly, the NIH acts as a producer of the work done for it by its grantee, while the FDA acts as a supervisor of work done privately and submitted to the FDA in its role as regulatory gatekeeper. Clinical data is a productive input for the NIH, but only a regulatory output for the FDA.

E. Resources and Disincentives

The regulatory response to adverse clinical trial events may not meet the public's expectations for safety. Only a small percentage of drug and medical device clinical studies are audited each year. Moreover, global research dispersion has directly affected regulatory resources. More drug approvals are relying on studies done outside the United States, where auditing visits cost more. As a result, with the same amount of audit resources available, fewer domestic site visits have been possible in recent years. FDA staff hope that future budgets will allow a greater number of audits, because the large number of non-hospital clinical sites has steadily grown each year.¹⁸¹

When audits of clinical studies do occur, the FDA's field auditors responsible for overseeing clinical trials of products sometimes criticize clinical investigators for: (1) inadequate records, (2) failure to follow protocols, and (3) failure to obtain an adequate informed consent document from each subject. On rare occasions, clinical investigators have been disqualified from future research for their violations of proper procedures.¹⁸² Although criminal prosecution for fraud is possible, this sanction is rarely employed.

Public expectations exceed resource-driven realities. Indeed, the public expectation of federal oversight of every clinical study or federal review of the safety of every test differs from the reality. When an injury occurs, it may not be recorded as study-related, or it may be reported as routine and filed away. The FDA may assign some reports for follow-up inspection by a field investigator, but the FDA's field

181. See Barton Interview, *supra* note 24.

182. Failure to adequately protect human subjects, or lack of integrity in the testing process, may result in this permanent prohibition against use of the clinical investigator. See FDA, *Disqualified/Restricted Assurance List for Clinical Investigators* <<http://www.fda.gov/oha/list2.htm>>.

staff is already spread thin with their caseload of other activities.¹⁸³ No remedy exists if a flawed study slips through the system undetected. Supervision of clinical research is considered to be a “discretionary function” depending on government priorities.¹⁸⁴ There is no remedy for a plaintiff injured as a result of the government’s negligent failure to supervise studies because the Federal Tort Claims Act precludes these suits.¹⁸⁵

Another systemic barrier to research monitoring is the approach the FDA takes to possible fraud in clinical trial records.¹⁸⁶ One example is the FDA’s approach to the signature of informed consent documents.¹⁸⁷ When a field investigator suspects that records were falsely prepared or forged, or when the FDA hears an allegation of fraud from a disgruntled employee, the file is transferred to another office. That office, the FDA’s Office of Criminal Investigations, is a separate branch of the FDA with powers of criminal search and arrest that takes over all alleged fraud cases. Therefore, the expertise of the field investigator with the clinical study data is no longer applied and the normal research quality reviews stop until after the completion of any prosecution.¹⁸⁸ This division between the audit process and the enforcement process means that within the FDA, the work of overseeing clinical research is now divided between monitoring for paperwork compliance and prosecuting for alleged fraud. This internal dividing line prevents communications across departments of the agency because the files are embargoed as potential evidence in a future criminal case. Once the criminal branch of the FDA takes the files, patient protection documents are unavailable to the administrative auditors and no further administrative FDA action is undertaken pending indictment or a decision not to prosecute.¹⁸⁹

183. See Barton Interview, *supra* note 24. The FDA’s workload has exceeded its resources for many years. See Frances O. Kelsey, *The Bioresearch Monitoring Program*, 46 FOOD DRUG COSM. L.J. 59, 60-61 (1991) (providing historical information on FDA monitoring programs).

184. See 28 U.S.C. § 2680(a) (1994).

185. See *id.* § 2680 (listing exceptions to the Federal Tort Claims Act).

186. See James T. O’Reilly, *More Gold and More Fleece: Improving the Legal Sanctions Against Medical Research Fraud*, 42 ADMIN. L. REV. 393, 402-06 (1990) (providing background on the enforcement process prior to the creation of the Office of Criminal Investigations).

187. See 21 C.F.R. § 50.20 (1999) (noting that the informed consent of the subject is required in FDA-submitted clinical trials).

188. Prosecutions are rarely undertaken and usually involve mail fraud counts. See, e.g., *United States v. Garfinkel*, 29 F.3d 451, 453 (8th Cir. 1994). When the FDA attempts a prosecution, it sometimes loses. See, e.g., *United States v. Smith*, 740 F.2d 734, 739 (9th Cir. 1984) (dismissing the prosecution and holding that investigators are not covered under regulations imposing criminal liability).

189. See Barton Interview, *supra* note 24.

F. *Effects of FDA Speed on Clinical Patient Protection*

A side issue is whether safeguards for patients suffer when testing is sped up and streamlined. There are no empirical statistics on the effects of faster medical product development clearance on the protection of human subjects.¹⁹⁰ Historically, the FDA rewarded inertia by risk-averse drug reviewers who kept harmful drugs off the market.¹⁹¹ By the early 1990s, when the AIDS crisis shattered the FDA's paradigm of cautious delay, a cultural revolution swept the drug research and review process into high gear.¹⁹² The FDA responded to legislative pressures with a "fast track" option for AIDS drugs clearance.¹⁹³ Congress gave the FDA specific timing deadlines for faster drug approval in return for more money and more personnel.¹⁹⁴ The FDA met its side of the bargain by concentrating on streamlined approvals of the sponsors' submissions with fewer internal delays. Along the way, product approval stages were compressed, data submissions reduced, funding for reviews increased and the method for clearing sponsors' drugs through each stage changed to computer-maintained logs and milestones.¹⁹⁵

During this period of accelerated approvals, the FDA's budget for clinical testing inspections remained virtually constant, although the number of sites to be reviewed had increased.¹⁹⁶ The likelihood that an individual clinical patient in a drug or device trial would have her records checked by a government inspector probably also decreased, but the absence of quantifiable data limits this probability to an informed speculation indicating that patient protective regulatory oversight was reduced.

FDA trends suggest an increased emphasis on the speed of product approval. The speed of drug approvals has increased so dramatically

190. Analyzing the factors, journalists concluded that there were significant conflicts between rapid testing and patient safety. See Kurt Eichenwald & Gina Kolata, *Testing Puts Value on Speed Above All*, N.Y. TIMES, May 16, 1999, at A34.

191. Drug reviews prior to the reforms of the 1990s emphasized caution and conservatism in estimating potential risk of a product. See O'REILLY, *supra* note 32, § 13.02 (covering the historical evolution of drug reviews).

192. See Nancy K. Plant, *Adequate Well-Controlled Clinical Trials: Reopening the Black Box*, 1 WIDENER L. SYMP. J. 267, 277 (1996) (describing changes in the FDA approval process).

193. See 21 C.F.R. § 314.520 (1999) (detailing accelerated approval of new drugs for serious illnesses).

194. See 21 U.S.C.A. § 379h (West 1999).

195. See <<http://www.fda.gov/cder>> (providing the FDA's extensive data on the implementation of time deadlines for review of medical research, which was supported by the PDUFA legislation).

196. See Barton Interview, *supra* note 24.

that the FDA won recognition for its innovation and efficiency.¹⁹⁷ Funding for the FDA's drug review personnel now largely comes from special statutory fees that are conditioned upon meeting goals of quicker product clearance.¹⁹⁸ In the past, however, the extra personnel fees almost exclusively funded product review and approval and did not add to the resources available for monitoring patient protections.¹⁹⁹

Congress successfully sped up the processing of clinical data during pre-approval reviews in order to hasten the approval of new drugs for diseases like AIDS. Based on that success, Congress expanded the fast track in 1997, expediting the FDA's review of drug clinical trials by limiting the FDA's ability to place new drug trials on "hold."²⁰⁰ The 1997 Congressional action created a virtual presumption of an experiment's approvability if the FDA failed to veto the proposed clinical trial within a very brief period following notice to the FDA of the planned testing.²⁰¹

For medical devices, Congress delegated the pre-testing clearance of most device experiments from the FDA down to the local IRBs.²⁰² Problems arising from this delegation resulted in more FDA guidance, but the FDA did not retake control of test clearance decisions.²⁰³ Streamlining the device approval steps for products like surgical devices allowed the FDA to devote more resources to the processing of approval submissions for the most serious risk devices.²⁰⁴ As a tradeoff for this efficiency, there is no governmental review of the safety of patients enrolled in many medical device studies.²⁰⁵

197. *See FDA's Drug/Biologic Review Reforms Selected as Semi-Finalist in Prestigious, Nationwide Award for Government Innovation*, HHS NEWS RELEASE (U.S. Dept. of Health and Human Services), Apr. 30, 1997, at 1.

198. *See* 21 U.S.C.A. § 379h (West 1999).

199. That situation, however, has eased since 1998-99. *See* Telephone Interview with Carolyn Hummel, Center for Drug Evaluation and Research, Food and Drug Administration (Aug. 16, 1999).

200. *See* 21 U.S.C.A. § 355(I)(3) (West 1999).

201. *See id.*

202. *See* 21 C.F.R. § 812.2(b) (1999).

203. *See* Less et al., *supra* note 120, at 968.

204. *See id.* The FDA has allowed the investigational device clearance process for risks that are less than "significant" to be managed by local institutional review boards, with no FDA involvement in deciding whether the physician or surgeon could perform human experiments with the experimental device. *See id.*

205. Nevertheless, the regulations require that the sponsor supervise the informed consent process, even though the FDA will not see the research. *See* 21 C.F.R. § 812.2(b)(iii) (1999) (requiring that "each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent . . . and documents it . . .").

The relationship between regulatory agency resources and the extent of federal oversight of testing safety came into clearer focus during the 1990s. The FDA gained more resources for the narrow task of expediting drug approvals. Accompanying this speed-related modification of approval procedures was the congressional grant of user fees for drug approval processes. These funds were used for approval measures, including the hiring of new physician reviewers, and for shortening further the duration of the FDA drug approval process.²⁰⁶ The FDA field investigation staff responsible for oversight of clinical trials, however, did not receive a corresponding increase. More funding in this area would have allowed more on-site audits of clinical trial institutions where patients had ingested experimental drugs. Until the spring of 1999, when investigative reporters for the New York Times uncovered safety problems among clinical testing patients,²⁰⁷ the absence of oversight for the newly accelerated drug approval process went virtually unnoticed outside of the FDA.

G. *Regulators and the New Intermediaries in Clinical Trials*

Obsolescence of regulations is a common problem in technology regulation, and patient protection rules are now overdue for a substantial overhaul.²⁰⁸ When Congress codified the FDA system for oversight of medical research experiments in the late 1970s, the utilization of study management organizations (“SMO”) was not yet a significant presence. These entities offer manufacturers full-service test placement and data gathering, saving manufacturers the costs of in-house studies. By the year 2000, a majority of U.S. clinical trials will have been conducted by SMOs, including clinical research organizations.²⁰⁹ Clinical research consumes an estimated four billion dollars annually, and three-quarters of that is industry-sponsored research.²¹⁰ The U.S. device and pharmaceutical companies have reduced overhead costs through outsourcing and delegating responsibilities to SMOs.

Government controls aimed at the industry become less meaningful when the regulations remain static and the industry’s structure significantly changes. The government’s patient protection

206. See 21 U.S.C.A. § 379h (West 1999).

207. See Eichenwald & Kolata, *supra* note 16, at A1.

208. See generally Moreno et al., *supra* note 98 (noting that there has not been a major revision of federal policies since 1981).

209. See 21 C.F.R. §§ 312.3(a) (1999) (providing the FDA’s definition of this category), 312.52 (1999) (noting that the use of the CRO to manage drug tests is permitted).

210. See OIG REPORT, PROMISING APPROACHES, *supra* note 1, at A1.

regulations²¹¹ implicitly assume a high level of institutional sophistication, perhaps assuming that distinguished scholars at elite medical colleges will be conducting the nation's medical experiments and publishing their results. That traditional perspective was once the norm,²¹² but the paradigm is no longer a reality. The majority of U.S. clinical research has been distributed to new and far-scattered testing sites by SMOs or manufacturers for reasons of expense control.²¹³ SMOs may merely view patient protection as part of the checklist of rules to be satisfied at a reasonable cost.

The elite clinical researchers still compete for NIH and other federal grant funds and draw patients to their specialized institutions. For these clinical researchers, the existing system of regulatory oversight remains suitable. Reexamination, however, is overdue. The issue of cost control is today's driving force in SMO selection of research sites, and the FDA accepts drug clinical studies from widely dispersed sites, as long as the resulting documentation appears to support the conclusion that the product has been shown to be safe and effective.

Another very pragmatic limitation on the FDA comes with the shift to non-academic venues for human clinical testing. FDA investigators visiting a large institution have multiple sources of information about the institution's practices and problems. The FDA can interview the institution's numerous quality assurance, clinical management and patient records personnel to determine the validity of the research.²¹⁴ As a 1999 New York Times investigative report demonstrated, it is much easier to conceal fraud in a small privately owned clinic, where an unscrupulous physician can earn huge amounts of money from a study management organization with unethical and fraudulent concealment of research problems and omissions.²¹⁵ This observation does not mean that "smaller is worse," but the FDA staff have legitimate concerns about their decreased ability to reach beneath the paperwork surface of a research study.

H. Government's Limited Scope of Control

The regulatory reach of NIH and FDA controls is defined by statutes and regulations that do not encompass all U.S. medical research. The

211. See Notice of Proposed Rule, 56 Fed. Reg. 28,003, 28,004 (1991) (providing the language of the preamble to the common rule).

212. See NBAC, *supra* note 13, at 17-18.

213. See Eichenwald & Kolata, *supra* note 6, at A34.

214. See Barton Interview, *supra* note 24.

215. See Eichenwald & Kolata, *supra* note 16, at A1.

FDA's jurisdiction is specifically tied to the presence of an "application for research or marketing permit," such as an investigational new drug exemption request.²¹⁶ If there is no application, there is no FDA jurisdiction. Likewise, the NIH lacks jurisdiction if the facility is not receiving federal grant funds.²¹⁷ A university or major teaching hospital is eager to comply with the set of NIH preconditions to ensure continued access to federal funds.²¹⁸ By contrast, a small clinic for arthritis patients operated by a few doctors will never see an NIH audit team. This becomes more significant as the latter venue becomes the more likely site for elderly patient participation in clinical trials. Legislation intended to regulate all clinical tests affecting interstate commerce was offered, but failed to pass in 1997.²¹⁹

Therefore, a medical research study privately funded that does not result in a new drug application or other FDA filing is beyond the control of federal officials. Its patients are subject to external protections of state medical licensing boards, tort law remedies, and the insurance risk management controls of the particular testing clinic or institution. Of course, while the regulatory system has finite boundaries, professional ethical norms apply to all forms of physician research on humans, and most physicians are ethically scrupulous about patient safety.

I. "Freedom" for Physicians to Experiment

There are significant factors limiting the FDA's jurisdiction over the performance of surgical and pharmaceutical experimentation. For example, there is the well-established FDA practice of allowing physicians to self-determine what drugs will be given to patients, without regard to the FDA-approved "indications for use"²²⁰ on the labels of the drugs. This has been widely accepted by tort case law; no separate tort liability attaches to the unapproved use itself.²²¹ The FDA carved out of its regulations an exception for use of a marketed drug "in

216. 21 C.F.R. §§ 312.3, 812.3 (1999) (discussing drugs and devices).

217. See 45 C.F.R. § 46.103 (1998) (providing that assurances are not required for sites that are not funded by federal funds).

218. See *id.* § 46.103(a) (requiring such institutions to provide a written assurance of their compliance).

219. See S. 193, 105th Cong. (1997).

220. See 21 U.S.C.A. § 352(f) (West 1999) (noting that the FDA requires the drug product to indicate in labeling the medical conditions for which it is intended, and that the absence of these indications from a label is a statutory violation).

221. See, e.g., *Staudt v. Froedtert Mem'l Lutheran Hosp.*, 580 N.W.2d 361 (Wis. Ct. App. 1998) (discussing the "off-label" use of surgical screws on the spine).

the course of medical practice.” This exception enables the physician to experiment freely with one drug or a combination of approved drugs, for whatever use, on persons in the physician’s “medical practice.”²²² Similarly, for surgeons, no FDA oversight attaches to the use of normal surgical methods utilizing medical devices for unapproved uses,²²³ or for use of a “custom” medical device.²²⁴ This absence of regulatory control allows the individual physician to engage in product experimentation without any interference by the FDA, as long as it is done on an individualized treatment basis rather than by or with the cooperation of a manufacturer or other commercial sponsor.²²⁵

For example, a New Jersey physician could give her patient aspirin for a liver tumor, or a Utah surgeon could try staples in the bowel of a colostomy patient although the staples had been made for use only on skin. By combining drugs or trying different uses and doses, the treating physicians may learn about what might work, and are free to submit their reports to journals. This form of experimentation occurs frequently with cancer patients, where much of the therapeutic regimens selected by physicians are not yet approved for that particular use by the FDA. This is known as “off-label” use, and is a form of tailored experimentation that the FDA has consistently given to individual physicians and surgeons without FDA approval.

The physicians’ exclusion from the FDA regulation of “the practice of medicine”²²⁶ is the political legacy of New York physician Dr. Royal Copeland, who served as a Senator while the New Deal-era legislative program was seeking passage of the Federal Food, Drug and Cosmetic Act. Senator Copeland’s legacy to his profession was the principle of federal non-interference with the prescribing decisions of state-licensed physicians.²²⁷ Senator Copeland felt that physicians should be allowed to choose their pharmaceutical remedies from any drug available, without regard to the uses for which the FDA had approved that drug. As the law evolved, the early legislative reports reflected Senator

222. See 21 C.F.R. § 312.3(b) (1999).

223. See *Staudt*, 580 N.W.2d at 363.

224. See 21 C.F.R. § 812.3(b) (1999).

225. See *id.* § 312.1-.160 (establishing that the FDA would not accept the observations of a physician who did not follow the adequate controls for comparative effectiveness research as a basis for product approval).

226. See *id.*

227. See 79 CONG. REC. 4858, 4859-64 (1935) (setting forth Senator Copeland’s role in which he invokes his experience as a physician to defend the limited reach of the new federal legislation).

Copeland's views.²²⁸ The result of this legislative history policy was that the FDA would not regulate choices made by individual physicians seeking to use an approved drug for an unapproved treatment in a patient.²²⁹ The FDA does not regulate the choice of an individual physician to use a drug for an "off-label" purpose once the FDA has approved the drug for any human use.²³⁰ This type of "off-label" use is widespread²³¹ and it is sometimes difficult to differentiate from regulated experimental uses.²³²

This FDA policy plays a role in drug experimentation. For example, a drug that was marketed for one treatment purpose could be the subject of medical journal reports by a physician who used the drug for another purpose. The published reports themselves, however, are not a basis for new drug approval,²³³ which would require more comprehensive, documented clinical testing.

Independent tests reported in a prestigious journal, however, may help the sales of a drug, even before the FDA authorizes the sponsor to assert that type of product effectiveness in the drug's approved labeling. Accordingly, the manufacturer's marketing efforts may potentially increase profits. This may occur through wider awareness in the medical community of the positive messages that physician-authors freely communicate about the additional effectiveness potential of these drugs. Until 1997, however, a drug manufacturer could not lawfully encourage physicians to make such additional uses of their drugs. In fact, the FDA policed these "off-label" claims to protect its authority to regulate manufacturer-initiated drug claims. Congress, however, allowed limited promotion of the results of these experiments in the

228. See S. REP. NO. 361, at 3 (1935).

229. See 21 C.F.R. § 312.3(b) (1999).

230. See Notice of Proposed Rulemaking, 37 Fed. Reg. 16,503, 16,503-04 (1972) (providing the language from the FDA preamble to proposed rule); see also William Christopher, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L.J. 247 (1993) (discussing the "off-label" use of drugs and control of this practice); David Kessler, *Regulating the Prescribing of Human Drugs for Nonapproved Uses Under the Food, Drug and Cosmetic Act*, 15 HARV. J. LEGIS. 693, 752-60 (1978) (setting forth the views of the future FDA Commissioner on the "off-label" use of drugs).

231. See generally 1 FRANK WOODSIDE, DRUG PRODUCT LIABILITY § 8B.05 (1999 ed.) (providing a helpful analysis).

232. In *Doe v. Sullivan*, 756 F. Supp. 12 (D.D.C. 1991), *aff'd*, 938 F.2d 1370 (D.C. Cir. 1991), soldiers opposed to the use of a vaccine that had not received FDA approval unsuccessfully sued to block the vaccine's use until the FDA had reviewed and approved it. See *id.* at 18. Such "off-label" use was part of the Desert Storm campaign against Iraq and was not an "experiment." Therefore, the FDA experiment rules did not apply. See *id.* at 15-18.

233. See 21 U.S.C. § 355(d) (Supp. III 1997), implemented by 21 C.F.R. § 312.1-.160 (1999).

1997 Food and Drug Administration Modernization Act.²³⁴ Therefore, market competition incentives are likely to draw more attention to such informal testing and its results for the product.

J. The FDA and Surgeons

The Copeland limitation of FDA jurisdiction over physicians' "practice of medicine"²³⁵ excludes federal regulators from oversight of the work of surgeons. The FDA controls the marketed devices they implant²³⁶ and the drugs they inject, but allows broad individual experimentation by surgeons. Adverse effects on the patient in the operating room are left to the tort system. The FDA does not interfere in any "off-label" administration of a drug or medical device by a surgeon.²³⁷ Further, informed consent rules of the FDA do not apply unless the surgery is part of a controlled clinical trial of a medical device or drug, the result of which is intended to be submitted for FDA approval.²³⁸ As a critic of the current system has observed, surgeons need no federal approval as long as their work is paid for by patients and their insurance companies.²³⁹

The implantable devices that are custom-made by surgeons for their individual patients enjoy a further, special statutory exception. Custom-made devices²⁴⁰ are those that surgeons uniquely create for use on individuals, as opposed to devices that are mass produced and may be used in any number of unknown persons. Custom-made devices do not require FDA approval and are not subject to FDA scrutiny of their administration to patients.²⁴¹

VIII. FAILURE OF THE TORT SYSTEM TO ADEQUATELY PROTECT ELDERS

A. Issues

Unanticipated harms to patients during drug and medical device testing may be viewed as failures. In this broad sense of "failure," the failure of a medical product experimental program may be attributable

234. See 21 U.S.C. § 360aaa (Supp. 1997).

235. See 21 C.F.R. § 312.3(a) (1999).

236. See *id.* § 812.1-.160 (requiring that a new medical device obtain prior clearance if it is implantable, unless "custom device" status applies, pursuant to 21 C.F.R. § 812.3).

237. See FDA Notice of Proposed Rulemaking, 37 Fed. Reg. 16,503, 16,503-04 (1972).

238. See 21 C.F.R. § 50.1 (1999).

239. See Charo, *supra* note 15, at A64.

240. These include specialized implantable devices adapted by surgeons for particular patients or operations. See 21 C.F.R. § 812.2(c)(7) (1999).

241. See 21 U.S.C. § 360j(b) (1994).

to either (1) a selection of inappropriate sets of persons²⁴² as test subjects; (2) deficiencies in the product or process used; (3) errors or omissions by health professionals; or (4) conduct by the health professional that was unreasonable and dangerous.

Both tort and regulatory systems respond to these failures, albeit imperfectly. The law's norms of liability and of regulatory responsibility correspond to these four types of failures. In some cases, a contractual remedy may also exist.²⁴³ Cases of institutional negligence in medical research usually involve items (1) or (3) above, where an institution had a legal duty to oversee the research performed on its premises.²⁴⁴ A products liability tort theory primarily focuses on item (2) above, providing a range of tort remedies.²⁴⁵ The jurisprudence of medical malpractice focuses generally on items (3) and (4).²⁴⁶ In those cases, the treatment of the individual patient should have conformed to norms of reasonable care in the community of similarly-situated medical practitioners, taking into account the experimental nature of the therapeutic device or drug being used. Regulators of products focus on items (1) and (2), while the professional disciplinary body for physicians responds to complaints in connection with items (3) and (4).

B. *Disincentives to the Contingent Fee Counsel*

Tort remedies for death or injury to an elderly person who was harmed by an experimental drug or device must overcome practical

242. For example, one of the enumerated protocols for a test may specify that a history of urinary tract problems disqualifies a person from testing a drug that has a potential to cause harm by accumulation within the body. That is, normal excretion is necessary to this type of study, and the admission of persons with a history of urinary problems means the physician failed to follow the protocol for the test.

243. See 21 C.F.R. § 50.25(a)(1) (1999) (establishing that experimental drug sponsors are required to inform patients regarding compensation in the text of the informed consent). Accordingly, a contractual obligation will usually exist. Any other contractual arrangement providing compensation but limiting remedies might be of dubious weight in the courts where a seriously ill patient is compelled to sign a standard form contract as a precondition to potentially beneficial therapy. Interesting policy questions will arise when such a case reaches the appellate courts.

244. The physician, not the hospital, has the duty under tort law to obtain patient consent. See *Staudt v. Froedtert Mem'l Lutheran Hosp.*, 580 N.W.2d 361, 363 (Wis. Ct. App. 1998).

245. The focus is on a "defect." See, e.g., RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 2 (1997) (establishing standards of liability for defective products).

246. See *Mink v. University of Chicago*, 460 F. Supp. 713 (N.D. Ill. 1978) (involving malpractice and battery claims where a woman was given a drug of which she was not aware); *Schwartz v. Boston Hosp. for Women*, 422 F. Supp. 53 (S.D.N.Y. 1976) (discussing informed consent and experimental treatment); *Burton v. Brooklyn Doctors Hosp.*, 452 N.Y.S.2d 875 (App. Div. 1982) (regarding liability for experiments involving drugs); *Valenti v. Prudden*, 397 N.Y.S.2d 181 (App. Div. 1977) (discussing liability for an experimental surgery).

barriers. First, the financial realities of modern tort litigation work against the successful pursuit of the elder's, or their estate's, lawsuit. Moreover, a systemic disinclination to value elders as tort plaintiffs results from the absence of the "lost earnings" portion of compensatory damages.²⁴⁷ In other words, an elderly retired person who has suffered no loss of wages would receive a smaller jury award than a young person who had a large putative "future earnings" value.²⁴⁸

Second, practical problems for elderly plaintiffs in civil litigation include memory lapses and pre-trial delays. The problem of witness recollection may arise where the disputed issue concerns an oral promise or reassurance of safety made at the time of the patient's initial visit to the testing site. Furthermore, significant delays in the resolution of their cause of action are the enemy of the elder plaintiff, because extended pretrial delays in litigation add uncertainties when the plaintiff is already aged and probably severely ill. Also, it may be difficult to retain competent counsel who is sufficiently funded for the complexities of a pharmaceutical or medical device case, even on a contingent fee basis in an elder's personal injury case. Elders' tort cases, when measured by settlement value, are less likely to be pursued by the most competent plaintiffs' counsel.²⁴⁹

C. Responses to Adverse Results

At the time a person is asked to participate in a medical experiment, they receive and sign an informed consent form prepared by the institution's lawyers. Some surgical patients are even asked to sign a waiver of their right to receive information.²⁵⁰ This act of consent has tort consequences as well as regulatory implications. When a death or serious personal injury results, there are at least four subsequent steps taken by the institution. The patient's consent is relevant to all four steps.

247. See OHIO REV. CODE ANN. § 2323.54(A)(1)(a) (West 1994) (describing lost income resulting from an injury as part of compensatory damages). Economic loss includes: "All wages, salaries, or other compensation lost as a result of an injury, death, or loss to person or property that is a subject of a tort action, including wages, salaries, or other compensation lost as of the date of a judgment and future expected lost earnings . . ." *Id.* This economic loss is considered part of compensatory damages. See *id.* § 2323.54(c)(1).

248. See generally O'REILLY, *supra* note 5 (exploring further issues addressed in this section).

249. There are certainly exceptions that occur, but plaintiff's counsel operating on a contingent fee may reduce their economic risk of loss by avoiding these less certain and less financially rewarding cases.

250. See 21 C.F.R. § 50.27 (1999).

First, the institution will use its internal processes to evaluate the cause of death. This evaluation is routine for hospitals or nursing homes that have standard operating procedures for documentation of death cases and may include a peer review of the surgeon's performance of the surgical procedure.²⁵¹

Second, the risk manager or another official may communicate with the institution's malpractice insurer. The insurer will be interested in limiting its liability and shifting causation to other parties, such as the manufacturer whose product was being tested. The content of the informed consent document will also be examined at that time.

Third, the institution will add documentation to the file concerning information that it received from the product sponsor and the time it received this information. Typically, hospitals will then assert that they functioned as a delivery point and not as a designer of the product, and therefore, they should be held harmless for any product-related harms.

Fourth, the IRB that authorized the study will receive notification as required by federal regulations of the "unanticipated problems involving risks to human subjects."²⁵² Once the FDA learns of a death or injury either from the required manufacturer's report²⁵³ or from the FDA's Medwatch hotline,²⁵⁴ it may investigate the circumstances of the death to determine whether appropriate FDA rules had been followed.

When viewed in its human dimension, serious injury or death caused by the experimental drug or device is tragic, though lauded as a noble sacrifice for the cause of medical advancement. The nobility of that sacrifice may be less apparent, however, to the grieving survivors and their lawyer.²⁵⁵ A cause of action asserting negligence or other tortious acts will claim that the tragedy could have been avoided. The most serious circumstance for a product sponsor arises after a series of deaths, when claims of product sponsor liability are intertwined with alleged physician malpractice in a pool of recriminations that demand

251. See 42 U.S.C. § 11137(b)(1) (1994) (stating that these peer review documents enjoy a federal statutory privilege).

252. 21 C.F.R. § 56.108(b)(1) (1999). This regulation provides in relevant part, that institutions "[f]ollow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of . . . [a]ny unanticipated problems involving risks to human subjects or others." *Id.*

253. See *id.* § 312.64(b).

254. See *id.* § 314.80(f)(3).

255. Nondisclosure of the experiment and subsequent harm to the patient can produce serious legal liability for the institution. See *Burton v. Brooklyn Doctors Hosp.*, 452 N.Y.S.2d 875 (App. Div. 1982) (challenging an institution when the physician did not disclose the nature of the experiment to the patient).

“who knew what when” and whether the knowledge could have precluded the patient’s harm. Hindsight alone does not cure disease, and some risks of experimentation are to be expected. Nevertheless, adverse results merit careful scrutiny in the context of a tort claim.

D. Tort Responses

The tort system exists to allocate the societal burden of individual injuries by recognizing duties of care by particular persons or groups, and by providing the injured person with remedies against breaches of that duty. The tort system should recognize that when injuries occur in medical research experimentation, the breach of duty can be actionable either against the physician, the institution, or the manufacturer. Medical products firms and their insurers are very conscious of product defect considerations with marketed products, but may be less attentive to evaluating a program of experimentation on a population of elderly patients.²⁵⁶ The FDA’s recent directives concerning drug testing on the elderly²⁵⁷ deserve close scrutiny by hospital and research organization risk managers because in these directives the FDA warns them of the potential for higher rates of adverse effects.²⁵⁸

Product liability issues facing the plaintiff include proving causation of the elder’s injury by a particular drug or a particular medical device. This may be difficult because an autopsy may be inconclusive about the link between an experimental dose of a drug and a patient’s harm, particularly if a period of time elapsed between ingestion of the drug and death.²⁵⁹ Other health problems associated with aging, such as kidney failure, may be cited by the defense as the actual cause of this “coincidental” event.²⁶⁰ Because the uncertainty regarding the effectiveness of a new drug or procedure is the very reason for conducting experimentation, the tort system is likely to weigh the benefit to society against the plaintiff’s assertion of negligence in an

256. Companies are becoming much more aware of the “subpopulations” from which test subjects are recruited. *See generally* Bonnie J. Goldmann, *A Drug Company Report: What is the Same and What is Changing with Respect to Inclusion/Exclusion of Women in Clinical Trials*, 48 *FOOD & DRUG L.J.* 169 (1993) (providing insight into this rationale).

257. *See* 21 C.F.R. § 201.57(f)(10) (1999).

258. *See id.*

259. *See, e.g.*, *Mink v. University of Chicago*, 460 F. Supp. 713 (N.D. Ill. 1978) (noting that the delayed onset of the adverse effects of drug ingestion makes later proof of causation difficult).

260. The proof of causation of an adverse drug reaction requires the plaintiff to know what other medications may have been in use; the defense will inevitably assert alternative causes of the plaintiff’s injury. *See, e.g.*, *RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY* § 2 (1998).

experimental surgery or medication claim.²⁶¹ Courts may find a certain degree of uncertainty permissible and refuse to hold manufacturers liable for an experimental drug given to an elderly test subject.

Proximate cause theory requires that plaintiffs must prove that “but for the action of the defendants,” the harm would not have occurred.²⁶² To decide that premise, jurors must evaluate the circumstances as they were known to the experimenting physician at the time of the test. Questions about prior medical history and concurrent use of other drugs are particularly important.²⁶³ The records on a clinical trial patient’s medical condition, however, may not supply all of the necessary data.

Proof of proximate cause, while difficult to show in most medical negligence cases, is even more challenging with elders because concurrent illnesses and medications may exacerbate the drug’s adverse effect. Juries may decline to compensate the already-ill plaintiff as they might compensate a healthier, middle-aged person. State tort reform laws have accomplished a great deal to limit damages for ephemeral, non-quantifiable “pain and suffering.”²⁶⁴ This trend is a disadvantage to the non-working elderly person whose diminished quality of life may not be reflected in a loss of future earnings. This results in a significantly less attractive “payout” for plaintiff’s counsel.

E. Role of Informed Consent

A very effective defense against products liability claims is the signed form document in which the patient has purportedly given “informed consent” to her participation in the experiment. Virtually all patients in experiments have been confronted with this routine document as a precondition to accessing the medical product.²⁶⁵ Consent forms are virtually universal in American clinical research, and their minimum content has been federally regulated since the adoption

261. *See id.* at § 6 cmt. f.

262. RESTATEMENT (SECOND) OF TORTS § 430 (1977).

263. *See* 21 C.F.R. § 201.57(f)(10) (1999) (noting that drug interaction is a serious risk).

264. *See, e.g.,* OHIO REV. CODE ANN. § 2323.54(B)(1) (West Supp. 1999) (limiting non-economic loss to \$250,000 or to an amount of three times plaintiff’s economic loss up to \$500,000) (invalidated as unconstitutional in August 1999 in *State ex rel. Ohio Academy of Trial Lawyers v. Sheward*, 715 N.E.2d 1062, 1095 (Ohio 1999)).

265. The issuer of the consent form generally sets the informed consent contents. The FDA, however, has set the minimum standards. *See* 21 C.F.R. § 50.20 (1999). In addition, the IRB then examines the adequacy of an individual investigator’s tailored consent form for the particular clinical experiment. *See* 21 C.F.R. §§ 56.109(b)-(c) (1999). The general requirements for informed consent are found in 21 C.F.R. § 50.20. The exceptions to informed consent are listed in 21 C.F.R. § 50.23 and § 50.24. The elements of informed consent are found at 21 C.F.R. § 50.25.

of uniform federal regulations in 1981.²⁶⁶ Although in theory its contractual terms are negotiable with the individual physician or hospital, the patient rarely has the option to alter the terms of an informed consent document.

The contract law concept of a “contract of adhesion”²⁶⁷ applies where the experimental drug may have unique benefits to an ill patient. A person desiring access to a new medication or new surgical technique for treatment of a terminal disease may not have the ability or incentive to negotiate the terms under which they enroll in the medication experiment. For these patients, “sign here or die” appears to be the only option.

A patient who arrives for surgery at a hospital confronts a stack of paperwork including history forms, consents, information sheets, billing forms, admission forms, and outpatient documents. Because little time may have been devoted to communicating the terms of the informed consent document pre-treatment, the patient may not be aware of its legal significance. Moreover, patients do not often think about a consent document as being truly “voluntary” once they have decided that the surgery is necessary.

Patient optimism also plays a role. Elders who are relatively healthy, ambulatory outpatients in a specialized type of clinic are likely to expect that their doctor’s choice of medication will work for them. Trust in the health care provider’s good faith in the care relationship grows more powerful as the care recipient feels more vulnerable. The elder whose doctor refers him or her to a specialist for surgery or an experimental drug is likely to accord that specialist a significant degree of deference, even extending to ready acceptance of experimental therapies.

The signed consent to participate in the experiment (or, in the case of surgery patients, the waiver of right to receive information) is a formidable barrier, making it extremely unlikely that the patient or their survivors will be able to successfully sue. Furthermore, a contingent-fee plaintiff’s counsel is significantly less likely to accept a case where the consent form appears to relate to the harm that occurred. A plaintiff challenging the experiment that resulted in the death of an elderly parent will have to argue that either: (1) the patient’s capacity to consent was weak or diminished; (2) her understanding of the content of the numerous forms presented to her before surgery was incomplete; (3) the document was written at a level above her ability to comprehend; or (4)

266. See Federal Policy for the Protection of Human Subjects, 46 Fed. Reg. 8975 (1981), *recodified*, 56 Fed. Reg. 28,003 (1991).

267. See RESTATEMENT (SECOND) OF CONTRACTS § 211 (1979).

the perfunctory oral explanation discounted risks of harm that the document laid out in fine print.²⁶⁸ Advocates of reform in informed consent practices have encouraged research sponsors to have auditors observe the consent process or otherwise to make clear the degree to which the test subject is accepting significant risks of harm.²⁶⁹

F. *Strict Liability Exclusions*

Tort law favors drug experimentation because of its social benefits.²⁷⁰ Specifically, strict tort liability is not applied to products used in normal medical research based on current social policy encouraging experimentation. If the physician or health professional caused the injury, the conventional claims are malpractice against the physician and negligence against the institution for failure to supervise. Alternatively, a claim could be filed against the institution for negligently granting privileges or credentials to the health professional. The intervening cause defense asserted by the manufacturer will frequently include assertions that the product was non-defective, and that it was the misconduct of the experimenter that caused the harm.²⁷¹

G. *The Informational "Shields" Against Plaintiffs*

The lack of adequate information is an initial roadblock to pre-suit investigation of an experimental drug-related adverse effect. This deficiency may result from the fact that institutional records may be either incomplete or inadequate. Alternatively, the records may not show the degree to which institutional managers knew of the particular problem encountered by the patient as a result of the test. For example, where an individual surgeon is experimenting with a new form of surgery and no federal funds are utilized, federal regulators will not become involved.²⁷² If fellow surgeons at that hospital disagree with the safety of that experimental procedure, the hospital's peer review committee allows a forum for discussion and possibly informal

268. In fact, in many cases patients had signed informed consent documents without ever reading them. See Wogalter et al., *supra* note 79, at 593; see also *id.* at 613 (addressing the psychological factors involved with signing consent forms).

269. See NBAC, *supra* note 13, at iv. If an independent third party auditor is not used, "less formal procedures" may be used to assess capacity.

270. See RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 6 (1998) (noting that prescription drugs, for example, receive special exclusion from strict liability).

271. See *id.* § 2 cmt. p. For a manufacturer to be liable, a product must have been put to a foreseeable use. The intervening cause occurs when the user of the product uses it in an unforeseeable way, thereby exempting the manufacturer from liability.

272. See Charo, *supra* note 15, at A64.

discipline. Peer review confidentiality shields these records from any inquiries about the collective awareness of a surgeon's misconduct.²⁷³

It is virtually impossible to get useful data on the incidence of errors that occur during surgical procedures using experimental techniques. It is somewhat less difficult to find data about human clinical trials of drugs or medical products because this data must be reported in the documentation eventually supplied to the FDA.²⁷⁴

Compounding the problem of lack of information is the fact that a plaintiff injured during surgery may not even know that the surgeon was conducting an experiment. Even if she suspects this, however, she might not be able to prove that the product sponsor knew of the nature and scope of the surgeon's activities because the contract between the drug/device sponsor and the researcher often is protected from discovery as a "trade secret."²⁷⁵

Effective political lobbying has also provided experimenters with greater shields from tort suits. Medical malpractice statutes generally provide great protections for surgeons. For example, statutory limitations on damages reduce the likelihood of large punitive damage awards against a surgeon or drug clinical investigator. In addition, the *Restatement (Third) of Torts* changes pharmaceutical and medical device liability by virtually precluding product liability for design defect.²⁷⁶ Moreover, state product liability statutes often shield drug/device marketers after the product has been approved.²⁷⁷ It appears that some state courts may be willing to regard the FDA forms of permission to experiment as the functional equivalent of product

273. See 42 U.S.C. § 11137(b)(1) (1994). The tradeoff implicit in the statute is that candor and frank evaluation at the level of the peer group of surgeons is beneficial to improved safety, although the potential lawsuit deterrence that could be obtained with the documents is lost.

274. See 21 U.S.C. § 331(j) (1994) (establishing that the public does not have access to private companies' experimental drug records). Moreover, litigants must obtain protective orders and then could have difficulty reconstructing the experiences of other test subjects in order to obtain the experimental drug records.

275. Protective orders may be sought upon a motion for trade secrets or other confidential research. See FED. R. CIV. P. 26(c)(7). Alternatively, the court is allowed to quash a subpoena that requires disclosure of trade secrets or other confidential research. See FED. R. CIV. P. 45(c)(3)(B)(i).

276. See RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 6(c) (1998). There cannot be a design defect if a physician could prescribe this drug or device for any purpose. This approach cuts off most design claims in strict liability. For an analysis, see JAMES T. O'REILLY, *PRODUCT WARNINGS, DEFECTS, AND HAZARDS* § 10.02(c) (2d ed. 1999).

277. See, e.g., OHIO REV. CODE ANN. § 2307.801(D) (West Supp. 1999) (denying punitive damages where the FDA approved the drug's label).

approval.²⁷⁸ Accordingly, a design liability cause of action is rarely available in the experimental injury context.

As design and manufacturing causes of action fade away, a plaintiff's only chance of recovery in damages is "failure to warn." A plaintiff's counsel, however, may decide that if the elder has signed an informed consent document, the elder's potential case will be declined as uneconomical to pursue. Therefore, any hope that tort law may provide a "safety net" for the weaknesses of regulatory law is futile. The tort system works against full compensation for elders injured in experimentation.

IX. PROPOSALS FOR CHANGE

There are several options that lawmakers and regulators could undertake if they wished to increase the current levels of protection for elderly persons against exploitation and injury in clinical experimentation. First, the FDA should reiterate the importance of patient protection when it implements changes to the drug and device approval process, similar to when it recently imposed obligations on drug manufacturers for drug testing on elderly persons.²⁷⁹ Next, periodic review of the safety of research practices should be reemphasized because such review is very important to sustaining patient protections in the face of cost-cutting pressures. Finally, elderly patients need reassurance that there will be thorough monitoring and follow-up care for adverse drug reactions.²⁸⁰

A huge disparity in power and resources exists between test sponsors and test subjects. As a safeguard for patients, a statutory or common-law tort standard of strict liability to fully compensate test subjects for physical harm resulting from the experimentation seems particularly sensible. Further, the regulatory agencies should clarify their rules and require sponsors to remedy harms caused by the sponsored experimentation. Patients should then be advised that if a problem

278. Cases that equate the FDA's preliminary screening of products with the exhaustive final approval decision are simply wrong in their misunderstanding of the FDA's scrutiny. *See, e.g., Gile v. Optical Radiation Corp.*, 22 F.3d 540, 541 (3d Cir. 1994) (holding that Medical Device Amendment ("MDA") to Federal Food, Drug and Cosmetic Act ("FDCA") preempts private cause of action when the FDA approves clinical investigation of an intraocular lens to replace a natural lens of the eye); *Evrtaets v. Intermedics Intraocular, Inc.*, 34 Cal. Rptr. 2d 852, 854 (Cal. Ct. App. 1994) (allowing FDA approval of experiments of medical devices to preempt state law negligence and strict liability claims).

279. *See* 21 C.F.R. § 201.57(f)(10) (1999) (labeling of prescriptions changed with easier access to information via "Geriatric Use" subsection on label).

280. *See* Owens et al., *supra* note 51, at 117.

associated with the drug or device develops, the research sponsor will compensate them for any harms that may result. Any compensation commitment stated in a consent form should be clear and graphically conspicuous. As well, sponsors should not be permitted to enforce exculpatory clauses that free the sponsor from liability for drug-related harms.²⁸¹ If these changes are effectuated through state law, a uniform law should be considered so that states are required to adhere to similar norms.

Additionally, clarity of informed consent forms is essential. A patient should receive a document that is clear, legible and which prominently sets forth language indicating that the drug or device is being used experimentally. In order to effectively address the issue of a patient's choice to participate, the rules and norms of informed consent should be revised by both the FDA²⁸² and the NIH.²⁸³ A prominent statement in plain language would make elderly persons more aware of the risks they undertake when they agree to be part of a testing program.²⁸⁴

States that are considering amendments to their products liability laws following publication of the *Restatement (Third) of Products Liability*²⁸⁵ should carefully craft exceptions in their statutes regarding design defects to address circumstances involving medical research. As the *Restatement* is currently written, no design defect claim is available against a sponsor of an experimental prescription drug or medical device.²⁸⁶ In crafting their laws, states should collect empirical data to test the current assumption that tort laws effectively deter medical misconduct. Different considerations arise particularly where the type of misconduct at issue is a carefully planned and implemented form of research. States should determine whether products liability changes would deter weaker practices without impairing useful research.

Furthermore, state medical licensing boards should serve a more aggressive policing role because unethical conduct in research on patients is a serious breach of state licensing codes. State licensing boards have the duty to monitor physicians' compliance with informed consent obligations.²⁸⁷ At the very least, failing to protect patients from

281. See 45 C.F.R. § 46.116 (1998) (noting that the NIH forbids exculpatory language).

282. See 21 C.F.R. § 50.20-.27 (1999) (FDA regulations).

283. See 45 C.F.R. § 46.116-.117 (1998) (NIH regulations).

284. See Wogalter et al., *supra* note 79, at 593.

285. RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY (1998).

286. See *id.* at § 6, cmt. c.

287. Cf. *American Academy of Pediatrics v. Lungren*, 940 P.2d 797, 843 (Cal. 1997) (stating the court's assumption that physicians will get valid consent or face state disciplinary proceed-

unnecessary surgical or pharmacological risk is a serious lapse of physician responsibility.

In order to provide blanket reform for elders in medical research, states also need to coordinate with federal agencies. Increased and improved supervision would be possible by combining the National Institutes for Health's Office of Protection from Research Risks with the FDA's Bioresearch Monitoring Program, thereby placing both the auditing and enforcement function in the U.S. Department of Health and Human Service's Office of Inspector General ("OIG").²⁸⁸ The OIG has the institutional power, status and incentives to effectively promote the interests of these research patients, although this change will create a need for increased funding for these protective functions.

Next, insurance carriers and reinsurers should be educated to ask appropriate questions of their insured hospitals and manufacturers regarding test subject protections. Insurers should confirm that these hospitals and manufacturers are aware of the tort liability of supervisors who fail to adequately control researchers.²⁸⁹

Moreover, hospital accrediting agencies should examine the extent of a medical research institution's IRB funding and resources, because regulatory agencies may not be able to perform a sufficient number of in-depth, on-site audits. The acknowledged problems of IRBs²⁹⁰ may be addressed with the powerful leverage of the accrediting bodies. If resources are deficient and corners are being cut to save money in research, as seems to be the case in many venues,²⁹¹ the rarity of regulatory deterring actions leaves a gap.²⁹² Hospital accrediting agencies should clearly express their disapproval of such cost-saving

ings).

288. This statutory office already detects and pursues fraud in program operations throughout the Department of Health and Human Services. Furthermore, it has the audit and enforcement staff to balance the scrutiny of routine compliance with the hammer against exceptional misconduct. See, e.g., OIG REPORT, A TIME FOR REFORM, *supra* note 91.

289. This may be a future growth area of "errors and omissions" liability for insurance carriers. This would be considered a "special risk" under state insurance standards. For examples of comparable risks, see N.Y. COMP. CODES R. & REGS. tit. 11, § 26.12 (1999).

290. See *supra* notes 84-104 and accompanying text; see, e.g., Wichman, *supra* note 89, at 98 (stating that on-site IRBs do not keep up with regulatory issues regarding reviews, that they are bogged down in paperwork instead of attending to protecting human subjects, and that they face a lack of guidelines and lack consistency among IRBs).

291. See Moreno et al., *supra* note 98, at 1956.

292. A very rare enforcement case halted 1000 studies, in large part because the IRB was so underfunded and overwhelmed that it did not adequately oversee the research. See Brainard, *supra* note 26, at A44.

techniques. This would scare hospitals into paying careful attention to the quality of clinical research at their institution.

To determine what overarching protections elders should receive, a “summit meeting” should be convened with representatives of groups such as the American Association of Retired Persons, the FDA, the NIH, the American Medical Association, the Pharmaceutical Research and Manufacturers Association and other recognized patient advocacy organizations, such as the American Cancer Society. The balance of interests involved requires careful and broad constituency involvement.

Ultimately, Congress may prefer to adopt legislation like the Human Research Subject Protection Act of 1997.²⁹³ This bill, had it successfully passed, would have required compilation of now-absent data and would have required the allocation of resources to IRBs. As one supporter of the bill observed, widespread, privately-funded human research performed without regulation stands in contrast to the uniform federal regulatory commands for animal research.²⁹⁴ Unfortunately, animals receive more adequate and more uniform protections than do the elderly in today’s society.²⁹⁵

X. CONCLUSION

The safety net of elderly patient protection in medical experimentation looks fine from a distance, but close scrutiny reveals several holes. Legal principles supporting the protection for patient safety during medical research are in place. The largest, most sophisticated academic institutions that once did most of the nation’s drug and medical device testing still adhere scrupulously to these norms. But the paradigm shift in modern drug and medical device research is to cut costs and disperse studies to smaller clinical sites. Abandoning the old paradigm diminishes some of the oversight protection that the conventional system has provided.

Cost concerns and other significant disincentives to the old-line, academic venues of drug and medical device testing led to reductions in protection for patient safety. This shift may disproportionately impact elderly patients. Today’s medical research industry lacks the time, the incentives and perhaps even the desire to conduct a patient-focused system of safety oversight. Cumulatively, these disincentives deter real protection.

293. See S. 193, 105th Cong. (1997) (dying without hearings at end of that Congress).

294. See 7 U.S.C. § 2131 (1994).

295. See Charo, *supra* note 15, at A64.

As the National Bioethics Advisory Commission observed, recent trends “present a challenge to create a regulatory framework that can protect individuals while allowing appropriate research and product development to flourish.”²⁹⁶ Moving toward assuring the protection of elders requires both the regulatory and tort systems to concurrently assist the injured elders and protect potential victims. Unfortunately, change often awaits a crisis, and the testing industry may deny the existence of a problem so long as certain, important factual data does not exist. The absence of a quantitative set of empirical data on the incidence of harm to elderly persons in research experiments is a problem for reform advocates.²⁹⁷ Ironically, just as a shortage of patients for testing would inhibit the finding of a drug’s effectiveness, the shortage of data about harm during experimentation may prevent the case for reform from gaining sufficient momentum. Reform could take the form of several statutory amendments, including more specific patient protections, constraints on physicians, and reinstatement of manufacturer and/or physician liability for harms caused during research. More adequate federal funding for a well-staffed inspectional effort to fully implement current laws and rules would bridge the gap until the laws can be improved.

But will laws be changed for the benefit of testing companies or for the benefit of patients? The lobbying power of physicians and surgeons is well recognized, and the medical profession is likely to oppose changes that would alter the present pro-physician tilt of the law of medical research. Revisiting the *Restatement (Third) of Products Liability* could help, but its post-hoc effect would not change much in real terms of patient exposure to harm. Rather, malpractice insurers of physicians and reinsurers of medical products companies should insist as a condition of coverage for experiments that any patient adversely affected in experimentation should be reported to regulators and corrections made where necessary.²⁹⁸

Tort law is evolving in ways that do not offer much financial incentive for an injured elderly patient to bring a cause of action against an experiment sponsor. In lieu of tort law reform, some reorganized and refocused regulatory presence may increase the likelihood that

296. NBAC, *supra* note 13, at 6.

297. See generally Moreno et al., *supra* note 98 (acknowledging, in suggested reforms, the absence of data).

298. Such a requirement would not expose insurers to greater liability. Rather, it is in the insurer’s interest to improve practices and keep bad doctors out of practice to reduce medical malpractice losses.

harms may be detected and avoided before they occur. The current system's paper trail audits, months or years later, are transparently seen as a paper tiger. If systemic safety problems expose elderly patients to harm, criminal prosecution is a proper response.

For the present, elders as "volunteers" within the research industry are being exposed to an increased volume of medical research and experimentation, while the systems touted as being useful for their protection are significantly flawed. Although these changes would benefit patient protection, it would be at the expense of increased delays and costs. The changes will need the concurrence of advocates for elders, doctors, regulators, and the tort system. Moving toward that set of changes is necessary, and the slow process of reform should begin now. The core principle of ancient medicine, "first do no harm" should be the watchword for research regulators of the twenty-first century.