

2010

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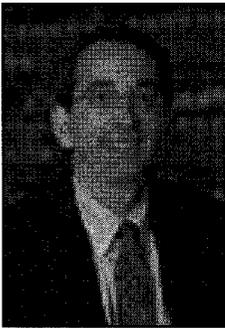
### Recommended Citation

Richard S. Saver *Medical Research Regulation after More than Twenty-Five Years: Old Problems, New Challenges, and Regulatory Imbalance*, 19 *Annals Health L.* 223 (2010).  
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## Medical Research Regulation After More Than Twenty-Five Years: Old Problems, New Challenges, and Regulatory Imbalance

*Richard S. Saver\**



Over twenty-five years ago, medical research entered a new regulatory era, resulting in more extensive oversight applied to a wider range of clinical trials. Protection of human subjects was, and continues to be, the primary justification for this regulatory shift. But whether the mission has been even partially accomplished remains an open question. While some contend that the existing regulatory framework inadequately protects research subjects, others worry about the considerable costs of compliance. Today's radically different research environment compounds and exacerbates these tensions. The research oversight system struggles with persistent old problems while addressing difficult new challenges, and balancing paradoxical concerns about under regulation and overregulation. This is a pivotal time.

### I. THE 1981 FEDERAL RESEARCH REGULATIONS

In 1981, the Department of Health and Human Services (HHS) and the Food and Drug Administration (FDA) substantially revised their research regulations, implementing various provisions of the National Research Act of 1974<sup>1</sup> and recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Among the major changes, the 1981 rules applied regulatory oversight to more clinical trials, specified what information should be disclosed to subjects, and provided detailed criteria concerning the standards for approving protocols. The 1981 rules also generally expanded the role of institutional review boards (IRBs), the research review committees that

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1. The National Research Act of 1974, Pub. L. No. 93-348 (1974).

approve and monitor clinical trials involving human subjects. This two-tiered approach so central to the 1981 regulations— detailed informed consent requirements plus IRB risk/benefit assessment and monitoring – has remained mostly unchanged and forms the basic framework for the current federal regulatory scheme.

## II. A CHANGING RESEARCH ENVIRONMENT

Meanwhile, a very different research environment has emerged since the promulgation of the 1981 HHS/FDA rules. First, the volume of clinical trial activity continues to increase at an astonishingly rapid pace, while research protocols have become more specialized and complex. As such, IRBs face daunting resource and capacity constraints to monitor research activity and accurately assess the probable risks. Second, money now plays a much bigger role in shaping the direction of medical research, with investigators, medical centers, and industry entering into complex financial arrangements to commercialize medical discoveries—creating potentially significant financial conflicts of interest. Third, research activity has moved away from academic medical centers to community physicians practicing in diffuse office settings, affecting both who conducts medical research and where it occurs.

## III. PERSISTENT OLD PROBLEMS

While the record is subject to differing interpretation, the new regulatory framework has likely improved clinical trial safety, as all stakeholders involved in medical research have become accustomed to the system of IRB review, adverse event reporting, and other safeguards. For example, a 2004 review of cancer drugs tested during Phase 1 clinical trials, considered the most dangerous phase of testing, concluded that, over a twelve year period, the odds of death from an experimental intervention dropped to less than ten percent of the earlier likelihood.<sup>2</sup>

Nonetheless, persistent problems remain. With regard to harm protection, while the likelihood of serious physical injury to subjects seemingly has been reduced, experimentation, by its very nature, presents unpredictable risks. The tragic death of Jesse Gelsinger during a gene therapy investigation at the University of Pennsylvania, a widely reported incident that brought new scrutiny to the research enterprise, demonstrates how things can, and still do, go horribly awry in clinical trials. Also, apart from physical injury, there is increasing recognition of the intangible harms research subjects endure such as affronts to dignity, breaches of

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2. Thomas G. Roberts et al., *Trends in the Risks and Benefits to Patients With Cancer Participating in Phase 1 Clinical Trials*, 292 JAMA 2130 (2004).

confidentiality, erosion of trust, financial loss, and frustrated access to care.

Boundary issues also continue to present problems. The distinctions between regular clinical services, true experimentation, and innovative care presumably falling somewhere in between, have, if anything become all the more confusing and blurred in the past twenty-five years. As an example, considerable litigation has been devoted to whether certain cutting-edge cancer care should be classified as experimental and, accordingly, whether and when health plans must pay for it. Meanwhile, clinical variation studies demonstrate wide differences in physicians' treatment selections, revealing the degree of experimentation and guess-work undertaken by physicians providing "regular" medical services. Unfortunately, the law has not helped in addressing the boundary confusion. Court opinions and statutory/regulatory directives have not clearly and consistently explained the different obligations arising under the doctor-patient relationship compared to the investigator-subject relationship.

These boundary confusion issues fuel ongoing informed consent concerns as well. Despite the research regulations' detailed information disclosure requirements, therapeutic misconception problems persist. Many patients still confuse experimentation with regular clinical care. Subjects also may be unaware that they can sometimes obtain the same services outside a clinical trial, such as with off-label use of an already approved drug. Unfortunately, the current oversight system frequently disappoints as a means of improving the quality of research consent. The typical consent forms found in research protocols are quite lengthy, full of boilerplate language, and difficult to comprehend, even after extensive editing by IRBs. Meanwhile, the regulatory fixation with subjecting written consent forms to repeated rounds of IRB review diverts energy and resources from more meaningful methods of monitoring informed consent, such as audiovisual material, patient ombudsmen, audits, and follow-up interviews with already enrolled subjects.

#### IV. NEW CHALLENGES

While such old problems stubbornly persist, the research system faces significant new challenges as well, including serious risk of both under regulation and overregulation. Legitimate concerns have been raised about IRBs' increasing workloads, limited resources, insufficient expertise, and lack of independence, suggesting that the IRB review system is simply too weak and ineffective to protect subjects. Yet, the oversight system has, at times, also appeared overly inclusive. Rather than substantive monitoring of what happens to subjects on a protocol, enforcement of bureaucratic and often obtuse procedures characterize much of an IRB's regulatory duties. The intense commitment of time and resources required to navigate all the

paperwork and secure IRB approval causes considerable frustration among research system stakeholders, including IRB members themselves. Instances of regulatory overkill deter beneficial experimentation and increase the costs of bringing new medical discovers into clinical practice.

The pervasiveness of financial conflicts also presents a significant challenge. According to recent studies, not only the investigators, but many of the reviewers sitting on IRBs and conflict of interest committees, have close financial ties to industry—calling into question the independence and integrity of the oversight system more generally. One of the preferred regulatory responses has been more compelled disclosure of such financial ties to research subjects. But so far this has not been a neat solution. Effectively conveying financial conflict information has proven quite difficult. Moreover, subject preference studies call into question how important subjects consider such information in deciding whether to participate in a research protocol, suggesting a primarily information-disclosure approach may be incomplete.

Further difficulties arise from reconsideration of why research subjects participate in clinical trials and what they really want. The traditional views regard subjects as altruistic, vulnerable volunteers who deserve special protection. But this view has proven too simplistic. Subjects participate in medical research not only to benefit medical progress but for numerous other reasons, including viewing clinical trials as a last resort when conventional treatments fail and wanting to be active in the face of serious disease. Thus, maximizing subject welfare has become a much more complicated question. As evidenced by the recent *Abigail Alliance*<sup>3</sup> litigation, certain patients want, above all else, access to investigational technology, and regard regulatory protections as paternalistic interference with their medical treatment choices.

Other traditional assumptions behind the regulatory model have been called into question as well, such as the dual loyalty problem. A long-standing concern has been that physician-investigators will feel pressures to sacrifice doing what is best therapeutically for the individual patient in order to advance their research goals. However, the dual loyalty problem is likely more complex in its actual effects. Recent studies suggest that certain physician-investigators are often more powerfully motivated by their clinical, not research, commitments. Thus, investigators have allowed patients to enroll in studies despite not meeting the eligibility criteria, or have deviated from the study protocol in terms of medication dosage amounts given to the subjects, all because they thought individual patients might benefit. Moreover, opportunistic research subjects have been known

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3. *Abigail Alliance for Better Access to Developmental Drugs v. Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007).

to “cheat” (not reporting symptoms, sharing medication, etc.) by disregarding a protocol’s procedures in order to maximize their individual treatment opportunities.<sup>4</sup> Unfortunately, such actions undermine the research’s generalizability and validity. Apart from protecting research subjects, additional regulatory attention is needed to protect the integrity of the research itself.

Finally, and perhaps most critically, the research oversight system now faces a possible trust crisis. Opinion polls suggest the public’s confidence in the research system has been eroding, a trend, no doubt fueled by intense media coverage of subject deaths at leading academic medical centers, regardless of how anomalous such episodes may be. Industry efforts to suppress negative trial results, as occurred in the recent Vioxx and Paxil drug trial scandals, have also contributed to trust erosion. A research enterprise that cannot depend on the trust and willing participation of individuals to serve as research subjects simply has no viable future.

#### V. WHAT LIES AHEAD

With nagging old problems and serious new challenges, the oversight system faces an uncertain future. Is it completely dysfunctional and irrevocably broken, as some critics complain? Not likely. It is easy to gloss over the system’s achievements as the regulatory framework’s vague standards, such as ensuring subjects’ ethical treatment and protecting them from harm, defy rule-like precision and make it difficult to evaluate performance through consistent benchmarks. Even more important, it is not clear whether better regulatory alternatives exist, and the history of medical research abuses cautions against a return to largely professional self-regulation. What does seem critical is that, moving forward, health law strives to develop smart regulatory responses that demonstrate flexibility, attention to the actual experiences of research subjects, and awareness of real compliance costs. Much important work remains to be done and these are interesting times indeed for thinking about the past quarter-century, and likely future direction, of medical research regulation.

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4. Charles W. Lidz, et al., *Competing Commitments in Clinical Trials*, 31 IRB: ETHICS AND HUM. RES. 1 (2009); Udo Schuklenk et al., *Terminal Illness and Access to Phase I Experimental Agents, Surgeries, and Devices*, 89 BRIT. MED. BULL. 7 (2009).

