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Gatekeeping and the FDA's Role in Human Subjects Protection

The FDA bears the responsibility to monitor clinical trials and protect human subjects from harm.

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Introduction to Human Subjects Regulation

Clinicians and clinical researchers are well aware of the importance of human subjects regulations in medical research. Just about any study conducted at a university medical center, a hospital, a contract research organization, or elsewhere must now pass the muster of an Institutional Review Board (IRB). IRB approval is necessary before the project is begun, in some cases before investigators can even apply for funding. This is as true of social science projects in anthropology, economics, epidemiology, political science, and sociology as it is of clinical or experimental research in medicine and psychology. The aggregate activity conducted under human subjects protections is staggering: every year thousands of IRBs in the US examine over 20 000 research proposals, and hundreds of thousands of experimental subjects and patients are presented with their legal human subjects' rights and sign consent forms stating that they understand these rights as they participate in the experiment [1].

Exactly how we got here and exactly what keeps us here—the evolution and maintenance of human subjects protections in clinical research—are not well understood. Our casual understanding, available from some published histories and a brief tour of the World Wide Web, is that current human subjects protections in medical research followed from the Nuremburg Code of 1947 and the World Medical Association's Helsinki Declaration of 1964 and have been supported by the evolution of ethical standards in the medical profession. These impressions are half-true but miss the more important feature of human subjects protections: their authorship and enforcement by the US Food and Drug Administration (FDA). The breadth and rigor of human subjects regulations that govern US clinical research are attributable mostly to the FDA rather than to the AMA or the National Institutes of Health (NIH) [2].

The Role of the FDA

The FDA is the primary author and enforcer of human subjects protection in the United States. The agency's role as gatekeeper to the prescription pharmaceutical and device markets in the US, combined with the implied powers that come with that role, make the FDA the most consequential force for human subjects protection. The FDA's veto power over product development gives pharmaceutical firms and researchers compelling incentives to cleave tightly to federal regulations and rigorous ethical standards. Just as important, the FDA has interpreted its authority over clinical research quite broadly, issuing detailed and comprehensive rules and aggregating inspection forces to monitor clinical investigators, laboratories, and IRBs and even to interview human subjects enrolled in clinical trials. The FDA has a life-or-death say, not just about products but also about IRBs, clinical investigators, and individual studies.

The FDA was involved early and often in human subjects protection. The FDA's Investigational New Drug Regulations of 1963 included requirements for informed consent and human subjects protections in clinical trials with investigational new drugs [3]. In 1971, 3 years before Congress passed the National Research Act (P.L. 93-348)

requiring institutional assurances of human rights protection and IRB review, FDA regulations already required IRB approval of all studies involving investigational new drugs or biologics [4]. After harmonization of these regulations with NIH/Health and Human Services in the 1980s, the federal government's *Federal Policy for the Protection of Human Subjects* (the "Common Rule") was adopted in 1991. In many ways, the Common Rule codified practices and collected rules that were adopted decades earlier by the FDA.

The FDA's formal capacity in regulating clinical research is uniquely complemented by the day-to-day field and enforcement activities that the agency devotes to human subjects protection. No agency at any level of government conducts more inspections of clinical researchers and IRBs than does the FDA. Again, this practice began quite early. After a trial monitoring program was run and observed from 1972-1974, the FDA launched its Bioresearch Monitoring Program in 1977, which included inspection of clinical investigators, biopharmaceutic laboratories, toxicology laboratories, and IRBs [5]. Such inspections reports consume the time of more than 30 FDA employees at headquarters and in field offices. When deficiencies are found, the FDA may issue a warning letter to institutions detailing "significant deficiencies" in IRB oversight. If the deficiencies are serious enough, the FDA can disqualify both the IRB and the clinical investigator.

Exploring the Significance of FDA Regulation

Just how intensive or exhaustive is FDA oversight? Data are insufficient to permit a good answer to this question, but some patterns from the past 2 decades can be gleaned from FDA and congressional reports. From FY1986 to FY1995, for instance, the FDA's Center for Drug Evaluation and Research conducted 1712 inspections of establishments for compliance with FDA informed consent requirements. From 1991 to 1995, the FDA issued an average of 158 IRB inspection reports per year. In the early 1990s, such inspections uncovered numerous violations of federal rules, most of them minor. Almost half of IRBs (48 percent) inspected from October 1992 to September 1994 failed to keep adequate minutes of their meetings, while more than one-third (36 percent) failed to promulgate adequate written procedures. Almost half (48 percent) were found to have operated without a quorum of members present.

From January 1993 to November 1995, the FDA found violations serious enough to merit a warning letter in 31 cases. The agency has never disqualified an IRB, but in response to FDA findings of serious noncompliance with federal regulations, research institutions have disbanded their IRB more than 60 times in the past 2 decades. The FDA can also disqualify clinical investigators for serious or repeated violations of agency regulations. This too has happened only rarely—just 19 times from 1978 to 1994, according to one FDA report—but this number understates the reach of FDA regulation. Over the same period more than 110 clinical investigators were sanctioned or have signed consent agreements with the FDA, a serious and embarrassing admission of negligence in clinical research that can hamper researchers' ability to attract further funding. The threat of reputation harm is sufficiently harrowing for clinical researchers and medical centers that even rare sanctions present sufficient incentives for most researchers to rigorously maintain human subjects protections [6].

The FDA cannot, of course, disqualify physicians from medical practice, nor can it prohibit universities from engaging in research. What backs up the FDA's human subjects regulations is its authoritative gatekeeping role in the pharmaceutical and medical device marketplaces. Since 1938, by federal statute, no new drug may be marketed or prescribed in the United States without prior approval from the FDA. Universities, medical centers, and research organizations that violate FDA regulations will simply lose business from sponsors that must conduct clinical studies to receive FDA approval. Since research funding is the lifeblood of any research endeavor, FDA sanctions can do enormous implicit and explicit damage to the careers and livelihoods of researchers and research organizations that violate federal law.

Before approving an Investigational New Drug (IND) application, the FDA requires researchers to submit and sign a formal statement that they will uphold prevailing ethical standards and that their institution's relevant parties will be notified of their study. FDA officials have the power to reject or terminate INDs (and hence terminate clinical studies) when the proposal presents an "unacceptable risk" to human subjects.

Conclusions

Determining whether FDA regulation of clinical trials is maximally effective in protecting human subjects is beyond my aims here. A certain answer to this question may be impossible, and better information would require intensive study of tens of thousands of clinical trials conducted over the past few decades. One thing that is certain, however, is that to the extent that any institutional force in the United States will be responsible for strengthening or weakening human subjects protections, the necessary and effectual action will probably be observed in the Food and Drug Administration.

The emergence and enforcement of human subjects protection in the US has been the product of efforts by many organizations, institutions, and individuals. Neither the NIH nor university research committees nor medical associations (as general as the AMA and as specific as the American College of Cardiology) can be ignored. Yet to think of the FDA as just one more player in the political and scientific arena of human subjects protection would also be inaccurate. With its gatekeeping power over medical products, its considerable inspection force, and its long-held statutory authority, the FDA is arguably the most powerful player in clinical research.

References

1. For some rough estimates of the number of IRBs, number of federally sponsored or regulated clinical trials, and number of human subjects participating, see the report of the General Accounting Office (GAO), *Protecting Human Research Subjects*, March 8, 1996 (GAO/HEHS-96-72), pp. 2, 6. In the past half-century, the total number of human subjects in medical and pharmacological research easily exceeds 10 000 000 and is perhaps much larger.
2. Casual and academic treatments of human subjects protections, including informed consent and the evolution of institutional review boards (IRBs), generally ignore or accord trivial treatment to the role of the FDA. For example, the National Cancer Institute's "A Guide to Understanding Informed Consent" (available at www.cancer.gov) discusses the Nuremburg Code, the Declaration of Helsinki, the 1979 Belmont Report and the unified 1991 Federal Code for the Protection of Human Subjects, but not the FDA.
3. In ongoing historical research, I have found evidence that many ideas and statements in the 1963 IND regulations were in fact hatched in the FDA's Bureau of Medicine in the late 1940s and 1950s, long before the thalidomide tragedy of 1960-1961. See Carpenter D, Moore CD. Robust action in a bureaucratic cohort: FDA scientists and the Investigational New Drug Regulations of 1963. Paper presented at the Yale University Conference on American Political Development, October 2004.
4. Current FDA regulations are summarized in 21 *Code of Federal Regulations* part 50 (Informed Consent), part 56 (IRB Standards), part 312 (rules on Investigational New Drugs) and parts 812 and 813 (investigational devices).
5. Food and Drug Administration. *FDA Information Sheets*, Rockville, Maryland, October 1, 1995.
6. Nightingale S, Bagley GP. FDA sanctions for practitioners for violations of clinical trial regulations and other misconduct. *Bulletin of the Federation of Scientists*. 1994;81:7-13.

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