

Review Essay

Is Human Subjects Research (Ethics) in Crisis?

Baruch A. Brody. *The Ethics of Biomedical Research: An International Perspective.* New York: Oxford University Press, 1998. 386 pp. \$49.95 cloth.

Jeffrey P. Kahn, Anna C. Mastroianni, and Jeremy Sugarman, eds. *Beyond Consent: Seeking Justice in Research.* New York: Oxford University Press, 1998. 190 pp. \$39.95 cloth.

Jeremy Sugarman, Anna C. Mastroianni, and Jeffrey P. Kahn, eds. *Ethics of Research with Human Subjects: Selected Policies and Resources.* Frederick, MD: University Publishing Group, 1998. 246 pp. \$19.95 paper.

These are heady days for the study of the ethical practices of human subjects research. Recent revelations and findings by the press, by regulators, and by those of us who study doctors and researchers suggest that the system of protection of human subjects has some cracks in it. In fact, one might conclude from the recent spate of attention that there is something of a crisis ongoing in the ethics of research.

A 2 February 2000 search on amazon.com shows that there have been more than sixty books published since 1995 dealing with research ethics issues. A contemporaneous search of the *New York Times* archives (nytimes.com/archives/) for the terms “research and ethics” yields 208 articles in the past year alone. In the past two years or so, the following cases have received very public airings in the press:

1. In a totally unprecedented flurry of enforcement activity, the National Institutes of Health (NIH) Office for Protection from Research Risks (OPRR) stopped research at Rush-Presbyterian-St. Luke’s Medical Center (AP 1998), the West Los Angeles Veterans Affairs Medical Center (Monmaney 1999; Hilts 1999a), Duke University (Stout 1999; Weiss 1999), the University of Illinois at Chicago (Guerrero and Herguth 1999; Grahnke and Ritter 1999), the University of Colorado (Hubler 1999), Virginia Commonwealth University (Mathews 2000), and most recently, the University of Alabama at Birmingham (Hansen and Spencer 2000; Hilts 2000). While there have been some substantive concerns relating to subject enrollment and informed consent, most of these sanctions have been levied because of sloppy and inadequate operation of institutional review boards (IRBs) and slow or inadequate response to OPRR’s concerns.
2. Researchers at Stanford University were permitted by the state in 1997 to test the use of Depakote in incarcerated adolescent males to see if the drug would reduce aggressive behavior (Weber 1999).
3. Researchers at the New York State Psychiatric Institute, the Mount Sinai School of Medicine, and the Research Foundation of the City University of New York came under fire for giving fenfluramine to young children, many of whom were Hispanic or African American. The children were at-risk younger siblings of child offenders identified by the researchers through court records (Hilts 1998a; Waldman 1999; Bernstein 1999).
4. In the early 1990s, plastic surgeons at the Manhattan Eye, Ear, and Throat Hospital performed a study in which different surgical face-lift techniques were used on the opposite sides of patients’ faces without securing IRB approval and without express patient consent (Hilts 1998b).
5. Most recently, the Food and Drug Administration stopped all gene therapy trials at my institution, the University of Pennsylvania, because of alleged shortcomings and violations of protocols, revealed in an audit prompted by the death of Jesse Gelsinger (Stol-

berg 2000a).¹ Gelsinger's death also prompted a revelation of at least six deaths in other gene therapy trials that had not been reported to the NIH, in violation of the law, because the investigators determined the deaths were caused by the subjects' disease and not the experimental therapy (Nelson and Weiss 1999; Stolberg 1999). Several institutions and foundations sponsoring genetic therapy research halted trials because of concerns about patient safety (Nelson and Weiss 2000; Nelson 2000). The public hearings also spurred the reporting to NIH of 652 adverse events in trials using modified adenoviruses (as used in the Penn trial), compared to only 39 that had been reported promptly as required by law (Stolberg 2000b). At this writing, the far-reaching ramifications of this case are hard to predict, but it may lead to substantial changes in the oversight of genetic therapy as well as other types of human trials.

What has been revealed is that the system of institutional oversight does not (and perhaps cannot reasonably be expected to) protect human subjects of research from any and all risks. Indeed, two studies published in the scientific (but not public) press last year showed that published human subjects research has not always been subjected to prior IRB review and approval by the investigators, and that institutions and journals are not adequately fulfilling their gatekeeping roles to ensure that researchers comply with ethical and legal requirements (Merz, Leonard, and Miller 1999; Ruiz-Canela et al. 1999). Other studies have raised serious concerns about the adequacy of IRBs to perform their oversight function, finding that they are overworked and insufficiently staffed to monitor ongoing studies, and that they are probably unable to identify the true risks of research as it is carried out (Inspector General 1998; Moreno, Caplan, and Wolpe 1998; Eichenwald 1998; Lazar 1999; Hilts 1999b). Others have noted that the IRB is an institutional entity, and it labors under a research-biased conflict of interest (Cho and Billings 1997).

What has also been revealed is that, despite substantial growth in NIH funding levels, human subjects research in support of commercial efforts, such as drug development, is extensive and seemingly growing. Given current financial pressures, academic medical centers and their faculty are increasingly reliant on commercial support for their research efforts. Concerns have been raised about payments to doctors and institutions for enrolling patients in research projects, which present substantial, and

1. The Penn Institute for Human Gene Therapy has posted extensive information on the Gelsinger death on their Web site at www.med.upenn.edu/ihgt/.

normally undisclosed, conflicts of interest that can undermine physicians' quasi-fiduciary duties to act in their patients' best interests (Eichenwald and Kolata 1999; Berens and Manier 1999). Concerns have also been raised about the incentives offered to research subjects, some of whom often cannot afford access and may be induced to participate in research as a form of health care (Kolata and Eichenwald 1999).

More troubling, academic-based researchers and their institutions are taking direct proprietary interests in intellectual property and technology transfer, as well as in holding direct equity stakes in corporations that will seek to commercialize new developments. As revealed by the recent close examination of gene therapy, commercial interests often shield adverse events from public view by a cloak of secrecy that may well be contrary to the public interest (Nelson and Weiss 1999). It is not at all obvious that pharmaceutical and biotechnology firms should be allowed to keep injuries or other facts about drug trials involving human subjects secret. Indeed, when a potential subject is presented with an informed consent form, all the material information about the trial is effectively placed into the public domain. Some drug companies have attempted to gag potential subjects with a nondisclosure agreement embedded in their consent forms. While my IRB steadfastly rejected these restrictions, I have little doubt that some IRBs permitted them (or why would the companies keep trying?).

The concerns enumerated above have garnered congressional attention as well, and in response, the Department of Health and Human Services (HHS) is moving the OPRR out of the NIH into the office of the secretary. This new office, the Office for Human Research Protections, will have a greater budget and more staff as well as greater independence. A bill just proposed would go further and move the office out of HHS entirely (HRPPA 2000). Despite the high-level concerns that have led to this change, there are rumors afloat that the current agency head, Gary Ellis, may be replaced by someone perceived to be less antagonistic toward the research enterprise. Given OPRR's recent spate of enforcement actions, if true, this could amount to a case of shooting the messenger (Wadman 2000).

There is a palpable tension between protecting human subjects and preventing abuses and reducing the regulatory burden on researchers so that biomedical science may progress. The perception that regulations and regulators may stifle research may also reflect a change in the tenor of research and, perhaps, a change in the public's perception of the benefits of research. Nonetheless, recent revelations may temper this enthusiasm.

With this foreground, the recent book by Baruch A. Brody and the one edited by Jeffrey P. Kahn, Anna C. Mastroianni, and Jeremy Sugarman identify and summarize the evolution of policies and emerging issues in research ethics. Both books are useful resources and each could be used as a core text for the human subjects portion of a research ethics class. Both books discuss a wide range of policies. Brody includes substantial appendixes containing the U.S. regulations, Council for International Organizations of Medical Sciences guidelines, and a sampling of policies from developed countries around the globe. The volume edited by Sugarman, Mastroianni, and Kahn collects a wide range of U.S. and multinational policy statements, providing a handy resource for IRBs and researchers alike.

Brody covers a lot of territory (topically and geographically), reviewing international laws and policies that range from using animals in research to epidemiology and genetics studies in humans. Both Brody and Kahn, Mastroianni, and Sugarman discuss policies that have evolved for the protection of vulnerable populations, including prisoners, racial and ethnic minorities, and children, and both address the underinclusion—no, the express exclusion—of women and, in particular, pregnant women. Both also discuss the inherent conservatism in clinical trial design, where greater risks may in fact be justified in cases of life-threatening illness for which there are no satisfactory therapies. These potential benefits may be large enough to permit the waiver of consent in emergencies, where existing therapies are viewed to be unsatisfactory or unproved (U.S. Food and Drug Administration 1996).

Brody's thesis is that there has been substantial convergence across numerous research policies in developed countries, such as those regarding the general principles requiring independent review and informed consent from subjects. Nonetheless, there are areas where policies are still evolving, such as in epidemiology and genetics, and others where discernable differences exist and are likely to remain. Differences may arise when there is no agreement about the moral status of the subjects of research, as he describes with the cases of animals and preimplantation embryos.

Kahn, Mastroianni, and Sugarman document a shift from a regulatory climate of protecting human subjects from the potential harms of research to one of granting greater access to the potential benefits of research. Research subjects have become “participants,” and researchers are known to characterize subjects as partners in the research enterprise. This, of course, has limitations: How many researchers would share with their subjects their financial gains resulting from research? Kahn and his col-

laborators assert that concerns regarding justice arise at all stages of research, encompassing planning and prioritizing research areas, fund allocation, research design (e.g., setting inclusion and exclusion criteria), subject recruitment and, arguably, subject remuneration for participation, injury, and past injustices, data collection and analysis, and publication. Different decision makers must address the justice issues inherent in these stages of the research enterprise. This suggests that everyone involved, from a congressperson to a research coordinator, needs to be aware of the ethical implications of their decisions.

The unanswered question resulting from both books concerns the actual conduct of research (and Brody foreshadows his next book with this very question). Before we heed calls to reduce regulatory burdens (Snyderman and Holmes 2000), we must examine how heavy the current regulatory load is and how effective the current system of oversight is. We need to know not merely whether researchers are complying, but, more fundamentally, whether there are ethical lapses that pose real risks to subjects. We need to know more about what is not being captured by the existing regulatory framework in order to determine whether and what types of modifications of the system are necessary.

As highlighted by the publicized cases, it is clear that research investigators retain a high level of autonomy and are relatively free of effective oversight of their actions. Indeed, a student of mine who was undergoing diagnostic GI biopsies was approached by her surgeon as she was emerging from her anesthetic fog and asked to consent to the extra samples he had just moments before taken for a colleague's research. This case of battery went unreported because my student felt dependent upon the doctor for continuing care.

It may well be that researchers need more training and access to ethics resources. Several institutions, including the University of Rochester and the University of Pennsylvania, are adopting compliance programs that will require investigators to pass a certification test in research ethics. Duke University, perhaps in response to its sanction last year, has created a tenure-track position in research ethics, with heavy responsibility for education of the medical center community. To spur compliance, the IRB at the University of California–San Diego developed a software system that identifies all papers published by university faculty, and faculty are sent memos asking them to document under which IRB approvals the published research was performed.

We also need to have greater insight to the functioning of IRBs. IRBs, like any bureaucracy, and particularly overburdened ones, run the risk of focusing on process instead of substance. During an IRB meeting of one

panel on which I sat, after we had rejected several protocols outright, our administrator remarked to the group that we should remember that next time it may be our protocol being reviewed. While acknowledging the conflict many of us would prefer to deny, this admonition also revealed a primary concern with getting research proposals approved. Outright rejection of protocols is uncommon, and one would assume that it would only be done for good cause.

IRB staff also have a good deal of de facto authority as process intermediary between researchers and IRB members. A colleague at a different institution related to me that her panel had resolved the issue of systematic exclusion of pregnant women from clinical trials by agreeing that pregnancy was not an ethical exclusion criterion from phase III trials involving serious or life-threatening conditions. She later learned that the research coordinators treated these modifications, which were made as comments and as changes to the consent forms, as mere suggested changes to the consent form, not as required changes to the study design. The coordinators would thus take exception to the IRB's consent form changes because they were not the institution's standard, and the IRB staff signed off on them. Thus a good deal of time of the IRB members was wasted, their ethical judgments were dismissed, and a long string of protocols were put in process without actual IRB approval. My colleague did not press the issue because of concern about her career, and she left the issue to be captured, if at all, in an audit.

IRBs must be a resource in research ethics to university faculty. They should be provided with the resources and the institutional commitment to enable them to provide substantive research ethics training to faculty and research staff, and they could preferably have staff for more direct involvement with investigators who need assistance in designing, planning, and carrying out research. There are movements afoot in professional organizations such as Public Responsibility in Medicine and Research and the Applied Research Ethics National Association to develop certification programs, which hopefully will provide training in substantive ethics in addition to procedural compliance.

In summary, much remains to be done to understand our current system of oversight of research using human subjects. And, with the NIH actively funding research in the area of research ethics (National Institutes of Health 1999), we may learn a good deal in the coming years. What we learn will hopefully be of use to policy makers who seek to improve ethical practices while ensuring that research proceeds.

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References

- Associated Press (AP). 1998. Regulators Suspend Chicago Hospital's Human Research. Associated Press State and Local Wire. 19 November.
- Berens, Michael J., and Jeremy Manier. 1999. Safeguards Get Trampled in Rush for Research Cash. *Chicago Tribune*, 5 September.
- Bernstein, Nina. 1999. Two Institutions Faulted for Tests on Children. *New York Times*, 12 June, B-5.
- Cho, Mildred K., and Paul Billings. 1997. Conflict of Interest and Institutional Review Boards. *Journal of Investigative Medicine* 45:154.
- Eichenwald, Kurt. 1998. Monitoring of Drug Tests Is Faulted. *New York Times*, 12 June, A-14.
- Eichenwald, Kurt, and Gina Kolata. 1999. Drug Trials Hide Conflicts for Doctors. *New York Times*, 16 May, A-1.
- Grahnke, Lon, and Jim Ritter. 1999. UIC Chancellor Quits after Research Furor. *Chicago Sun-Times*, 10 September, 16.
- Guerrero, Lucio M., and Robert C. Herguth. 1999. Human Tests Halted; UIC Projects Suspended after Probe. *Chicago Sun-Times*, 28 August, 1.
- Hansen, Jeff, and Thomas Spencer. 2000. UAB Research Suspended: NIH Cites Problems with Review Board, Charges Numerous Flaws. *Birmingham News*, 21 January.
- Hilts, Philip J. 1998a. Experiments on Children Are Reviewed. *New York Times*, 15 April, B-3.
- . 1998b. Study or Human Experiment? Face-Lift Project Stirs Ethical Concerns. *New York Times*, 21 June, A-25.
- . 1999a. VA Hospital Is Told to Halt All Research. *New York Times*, 25 March, A-25.
- . 1999b. In Tests on People, Who Watches the Watchers? *New York Times*, 25 May, F-1.
- . 2000. U.S. Halts Human Research at Alabama. *New York Times*, 22 January, A-12.
- Hubler, Eric. 1999. FDA Move Halts Local Research: Thousands of Projects Suspended at Six CU-Affiliated Institutions. *Denver Post*, 24 September, A-1.
- Human Research Protection and Promotion Act of 2000 (HRPPA). H.R. 3569, 106th Congress, 2d session.
- Inspector General, Department of Health and Human Services. 1998. Institutional Review Boards: A System in Jeopardy? Publication OCI-01-97-00190, June. Washington, DC: U.S. Department of Health and Human Services.
- Kolata, Gina, and Kurt Eichenwald. 1999. Stopgap Medicine: For the Uninsured, Experiments May Provide the Only Treatment. *New York Times*, 22 June.
- Lazar, Kay. 1999. Medical Risks: Ethicists: Clinical Trials' Safety Net Full of Holes. *Boston Herald*, 27 June, 6.
- Mathews, Jay. 2000. Father's Complaints Shut Down Research: U.S. Agencies Act on Privacy Concerns. *Washington Post*, 12 January, B-7.
- Merz, Jon F., Debra G. B. Leonard, and Elizabeth R. Miller. 1999. IRB Approval and Consent in Human Tissue Research. *Science* 283:1647.

- Monmaney, Terence. 1999. VA Hospital's Ethical Nightmare: Morality and Medicine Collide at West L.A. Facility, Where Probe about Informed Consent Clouds Research. *Los Angeles Times*, 25 March, 1.
- Moreno, Jonathan, Arthur L. Caplan, and Paul Root Wolpe. 1998. Updating Protections for Human Subjects Involved in Research. *Journal of the American Medical Association* 280:1951–1958.
- National Institutes of Health. 1999. Research on Ethical Issues in Human Studies. PA/99-079, 31 March.
- Nelson, Deborah. 2000. More Gene Therapy Experiments Are Suspended: Hospital, Patient Groups Cite Safety Concerns. *Washington Post*, 8 February, A-2.
- Nelson, Deborah, and Rick Weiss. 1999. NIH Not Told of Deaths in Gene Studies: Researchers, Companies Kept Agency in the Dark. *Washington Post*, 3 November, A-1.
- . 2000. Earlier Gene Test Deaths Not Reported: NIH Was Unaware of “Adverse Events.” *Washington Post*, 31 January, A-1.
- Ruiz-Canela, Miguel, Miguel Angel Martínez-González, Enrique Gómez-Gracia, and Joaquín Fernández-Crehuet. 1999. Informed Consent and Approval by Institutional Review Boards in Published Reports on Clinical Trials. *New England Journal of Medicine* 340:1114.
- Snyderman, Ralph, and Edward W. Holmes. 2000. Oversight Mechanisms for Clinical Research. *Science* 287:595–596.
- Stolberg, Sheryl Gay. 1999. A Death Puts Gene Therapy under Increasing Scrutiny. *New York Times*, 4 November, A-24.
- . 2000a. Gene Therapy Ordered Halted at University. *New York Times*, 22 January, A-1.
- . 2000b. Agency Failed to Monitor Patients in Gene Research. *New York Times*, 2 February, A-19.
- Stout, David. 1999. Citing Safety, U.S. Stops Human Research Aid at Duke. *New York Times*, 12 May, A-20.
- U.S. Food and Drug Administration. 1996. Protection of Human Subjects: Informed Consent and Waiver of Informed Consent Requirements in Certain Emergency Research: Final Rules. 61 Federal Register 51497-51531, 2 October.
- Wadman, Meredith. 2000. Head of U.S. Watchdog Faces Uncertain Future. *Nature* 403:353.
- Waldman, Amy. 1999. U.S. Faults Medical Study at CUNY and Mount Sinai. *New York Times*, 17 May, B-3.
- Weber, Tracy. 1999. Drug Test on Teenage Inmates Probed. *Los Angeles Times*, 16 August, 1.
- Weiss, Rick. 1999. U.S. Halts Human Research at Duke. *Washington Post*, 12 May, A-1.