Taking the "I" Out of IRB — and Putting "Community" In

by Mary Faith Marshall

If one looks back on the history of American research ethics, a bold pattern emerges. Since World War II, about every twenty years or so a breach of the social contract between investigators and human research subjects galvanizes public and professional interest in the ethical foundations and oversight mechanisms governing research with humans.

Since 1945, the theory and practice of research ethics have evolved, and continue to do so. Charles McCarthy (who holds the true institutional memory of research ethics in the United States) beautifully details this pattern for us in an unpublished article that he prepared for the National Bioethics Advisory Commission.

The process looks something like this: professional whistleblowing or coverage in the popular press raises public and professional alarm of particularly egregious ethics violations. Examples include coverage of the Nuremberg Trial,[1] Henry Beecher's publication of "Ethics and Clinical Research,"[2] the *New York Times* exposure of the public health service syphilis study,[3] the University of Pennsylvania/Gelsinger gene transfer case, and the *Washington Post* series on international clinical drug testing abuses.[4]

The government responds with hearings, expert panels, and appointed commissions. Guidance, such as the *Belmont Report*,[5] and oversight mechanisms, such as regulations governing federally funded research with humans, requirements for Institutional Review Boards, and establishment of the Office for Human Research Protections emerge. Thus, as with any field of applied ethics, the process of research ethics is one of evolution — of reaction and adaptation.

Adapt it must, for the research enterprise is changing dramatically. Between 1986 and 1995, federal funding for biomedical research almost doubled, with half of those dollars allocated to academic research, and much of that portion allotted to medical schools. During the same period, expenditures in the private sector tripled; and among pharmaceutical companies expenditures rose by a factor of fourteen. Private-public research partnerships have emerged as a result of several factors. In spite of increased federal research dollars, clinical investigators face constraints imposed by managed care and loss of clinical revenues that have previously been "cost-shifted" to support clinical research by medical school faculty. There is a growing expectation that the research arm of academic medicine must, like the clinical arm, be a revenue source. Thus, there are new alliances with industry, especially in the realm of technology transfer.

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In addition, industry is reaching far beyond the academic medical center, its traditional partner, to private contract research organizations and private physician networks to help operate clinical trials. The percentage of industry-sponsored clinical trials in academic medical centers fell from 80

percent in 1991 to only 40 percent in 1998.[7] Large, multicenter trials are now the norm for clinical trials. The days of a single clinical investigator conducting a single trial are drawing to a close.

The Explosion of New Technologies

Further complicating the research oversight arena is the explosion of knowledge resulting from new technologies. The mapping of the human genome and gains in information technology reconfigure the research knowledge curve from linear to exponential. Freeman Dyson, professor emeritus of physics at the Institute for Advanced Studies at Princeton University, predicts that the next scientific revolutions will be technological, not conceptual; they will be tool-driven by the Internet, the genome, and the use of solar energy.[8]

Computer innovator Ray Kurzweil predicts that by 2029 direct neural pathways for high bandwidth connections between computers and the human brain will enhance visual and auditory perception, memory, and reasoning. A $1,000 unit of computation (1999 dollars) will equal the computing capacity of 1,000 human brains; by 2059 the same unit of computation will equal the computing capacity of all human brains. Distinguishing between a human and a machine will be difficult for an outside observer. By the end of the century, a penny's worth of computation will have a billion times greater computing capacity than all humans on earth.[9] We will, according to Kurzweil, be entering the post-carbon era in which "life-expectancy is no longer a viable term in relation to intelligent beings. Carbon-based human cellular processes will be replaced by electronic and photonic equivalents."[10]

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Such new knowledge poses new challenges for ensuring the safety of human (or other) research subjects. The forbidden knowledge question, "Should I know this and what do I do with what I know?" threatens the traditional risk/benefit calculus used to assess the adequacy of research safeguards. The use of genetic information will have implications for research subjects, their family members, and society at large. Issues of privacy, possibilities for enhancement, and the concept of "normal" will be fundamentally challenged. Conceptions of self, humanity, and individual rights will receive an even greater challenge as artificial intelligence evolves and eclipses human intelligence in the coming decades.

The Reform of Research Oversight

Back in the year 2001, however, we are mired in yet another research ethics crisis resulting from an unhappy confluence of harms to research subjects and gross violations of regulations governing human subjects research. In her *NEJM* Sounding Board article, "Protecting Research Subjects — What Must Be Done (a wake-up call to the profession)," the former secretary of Health and Human Services, Donna Shalala laments:

> I did not expect, or want, to complete my tenure as secretary of health and human services by raising questions about the safety of patients in clinical research. However, recent developments leave me little choice.
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> Unfortunately, the public's confidence in our work, our competence, and our ethics has been seriously shaken by the death of 18-year old Jessie Gelsinger in a gene-transfer trial at the University of Pennsylvania in which human subjects were not adequately protected and which represented the appearance of substantial conflicts of interest. Moreover, this young man's death led to the discovery by the NIH of many hundreds of unreported adverse events among volunteers enrolled in gene-transfer experiments. The failures to report adverse events properly to the NIH

occurred despite the compliance of the gene-therapy researchers with Food and Drug Administration (FDA) reporting requirements.[11]

In her article, Secretary Shalala promised major governmental reform of the system for protecting human subjects. She also challenged all those involved in the performance of human subjects research to "take the responsibility and necessary actions to strengthen the conduct of research at their institutions."[12]

Secretary Shalala's article attests to an inadequate, if not broken, system of human subjects protections. Her concerns are not new. Indeed, they were clearly articulated in a 1997 report by the National Bioethics Advisory Commission to President Clinton identifying the following key areas of concern:

1. Federal protections for persons serving as subjects in research do not yet extend to all Americans.
2. Despite widespread implementation of federal regulations by those departments and agencies sponsoring substantial amounts of biomedical research, a number of departments and agencies who sponsor primarily non-biomedical research or little research overall have failed to implement fully these federal protections.
3. Federal protections do not always include specific provisions for especially vulnerable populations of research subjects.
4. Many federal agencies find the interpretation and implementation of the Common Rule confusing or unnecessarily burdensome.
5. Federal protections are difficult to enforce and improve effectively throughout the Federal government, in part because no single authority or office oversees research protections across all government agencies and departments.
6. New techniques are needed to ensure implementation at the local level.[13]

Many of these concerns have or are being addressed by changes made by Secretary Shalala. The former Office of Protection from Research Risks — now known as the Office for Human Research Protections — has been moved from the NIH to the Office of the Secretary, DHHS; and its Director, Greg Koski, PhD, MD, reports directly to the Secretary. On the advice of a committee convened by former NIH director Harold Varmus, a new federal advisory committee — The National Human Research Protections Advisory Committee — has been formed.[14] The committee is chartered to advise DHHS, the OHRP, the Federal Agencies under the common rule, and the academic and research communities on human subjects protections. The Institute of Medicine, at the behest of the Office of Human Research Protections, has convened a committee for "Assessing the System for Protecting Human Research Subjects." The fast track component of the committee's charge is to evaluate proposed standards for the accreditation of human research protection programs.

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Attention to research integrity issues has not focused solely on human subjects research. The Office of Research Integrity has issued a new policy on the Responsible Conduct of Research that outlines broad and concrete core educational requirements for faculty, students, and staff involved directly in research. Under the new policy, training requirements have been extended to include all intramural and extramural staff engaged in research with Public Health Service Funds, including all animal, human, and basic science research.

Certification of investigators and IRB members is a mechanism under discussion in various national arenas. These are some of the federal initiatives for upgrading human subjects protections. Others that may emerge will likely be informed by two themes. First, the notion of systems or programs of human research protections rather than a narrow focus on IRBs; and second, increased professionalism of investigators and those with oversight responsibilities. Thus, the emerging concepts are the accreditation of human research protection programs (comprising senior administrators, investigators, IRBs, and research subjects) and certification of individual researchers or IRB members.

The Research Integrity Project

In response to Secretary Shalala's challenge to those involved in research at the local level, the Midwest Bioethics Center's Kansas City Initiative to Promote Integrity in Research (hereafter, the Research Integrity Project) is a new venture that is uniquely well positioned to react and adapt — and thus evolve — to national and local changes in the research environment.

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The Research Integrity Project complements the work of the Kansas City Area Life Sciences Institute to create ongoing alliances among public, academic, and healthcare institutions, and industry to promote the safety of human subjects research and the integrity of basic science research. Midwest Bioethics Center's initiative includes the institutional participants in the Life Sciences Institute: Midwest Research Institute, the Stowers Institute for Medical Research, the University of Kansas Medical Center, the University of Missouri-Kansas City, Children's Mercy Hospital, and St. Luke's Hospital, plus other local and regional academic institutions and healthcare providers.

The Kansas City Area Development Council plans to make Kansas City one of the top ten centers in the nation for biomedical research within the next ten years. To this end, it has pledged to raise $300 million in the next three years to strengthen the biosciences infrastructure and attract top scientists to the region.

The key strategies of the Research Integrity Project are to

- address the ethical issues of life sciences research;
- develop and deliver curricula on research integrity, including the responsible conduct of research and the protection of human subjects;
- provide consultation services to regional institutional review boards; and
- provide outreach services to the community.

The Research Integrity Project is organized as follows:

- *The Institutional Review Board Consortium* will provide educational resources and training for review board members, help develop policies and guidelines, and address common administrative issues. The Consortium includes representatives from all thirty-one of the major Kansas City Area institutions involved in research. The consortium may also consider the development of several "community" or "Uber-IRBs." These newly evolved review boards will be, in a sense, chimeras of local IRBs and independent review boards.
- *The Ethics of Research Work Group* has fast track and long-term objectives. The fast track goal is the development of Responsible Conduct of research (RCR) and other core curricula for

those engaged in research or research training and graduate level academic courses on topics related to research ethics. The longer term goal is to provide guidance on evolving issues in research ethics through scholarship in the form of position papers, articles, guidelines, or reports that are commissioned by community investigators, research institutions, IRB members, or public groups.

- *A community initiative* through which the Research Integrity Project team will develop curricula for public audiences to enhance their understanding of research methodology, ethical issues in research, professional integrity, and the role of the research subject. In addition there will be an educational strategy targeted to secondary school students to advance their understanding of biosciences research and issues in the responsible conduct of research. It will include the development of a Kansas City Youth Advisory Board. Ruth Levy-Guyer, PhD, director of the High School Bioethics Curriculum Project at the Kennedy Institute of Ethics will oversee this component of the project.

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- *Service and consultation* to assist institutions to prepare for and evaluate compliance with federal regulations and requirements governing human subjects research and to provide an objective forum for problem solving and consultation on request.

Guiding the project team's efforts is an outstanding National Advisory Council. Its members include Greg Koski, PhD, MD, director, Office for Human Research Protections; Ruth Levy-Guyer, PhD, director of the High School Bioethics Curriculum Project, the Kennedy Institute of Ethics; William B. Neaves, PhD, president and CEO, the Stowers Institute for Medical Research; Marion Grey Secundy, PhD, director, National Center for Bioethics in Research and Medicine, Tuskegee University; John C. Fletcher, PhD, professor emeritus of Bioethics at the University of Virginia; and Jeremy Sugarman, MD, MPH, MA, director, Duke Center for the Study of Medical Ethics and Humanities.

The project staff welcomes your suggestions. Check out our website <www.midbio.org> and let us hear from you! After all, as John Fletcher is fond of saying, "Ethics is everybody's business!"

Notes

1. *U.S. v. Karl Brandt, et al.*, ("The Medical Case") *Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law 10. Nuremberg, October 1946 – April 1949.* 2 vols. (Washington: U.S. Government Printing Office). See also *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation* by George Annas and Michael A. Grodin (New York: Oxford University Press, 1992).
2. Henry Beecher, "Ethics and Clinical Research," *NEJM* Volume 274(24) (June 1966), pp. 1354-1360.
3. J. Heller, "Syphilis Victims in U.S. Study Went Untreated for 40 Years." *New York Times* July 26 A1.
4. The *Washington Post* series ran from Sunday, December 17, 2000, through Friday, December 22, 2000. Headlines comprised: "Exporting Human Experiments," "Overwhelming the Watchdogs," "Failure of Consent," "Harvesting China's Blood," "The Global Drug Lab," and "Perils of Placebos."
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6. National Bioethics Advisory Commission. *Summary of Draft Recommendations: Ethical and Legal Policy Issues in Research Involving Human Participants*. December 2000: 4-5.
7. Ibid.
8. Freeman J. Dyson, *The Sun, The Genome, and the Internet: Tools of Scientific Revolutions* (New York: Oxford University Press, 1999).

9. Ray Kurzweil, *The Age of Spiritual Machines: When Computers Exceed Human Intelligence* (New York: Penguin Books, 2000).
10. Ibid, p. 280.
11. Donna Shalala, "Protecting Research Subjects – What Must Be Done," *NEJM* 343(11) (September 2000), 808-809.
12. Ibid.
13. Letter from Harold T. Shapiro, NBAC, to William J. Clinton. May 4, 1999. Available at <http://bioethics.gov/letter.htm>.
14. *Report of the Advisory Committee to the Director, NIH* from the Office for Protection from Research Risks Review Panel, June 3, 1999.