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# Bioethics Inside the Beltway: IRBs Under the Microscope

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# Bioethics Inside the Beltway: IRBs Under the Microscope

**Abstract**
The spring and summer of 1998 were seasons in the sun for institutional review board (IRB) aficionados. Rarely have the arcana of the local human subjects review panels been treated to so much attention in both the executive and the legislative branches of government, not only at the federal but also at the state level. And it looks as if the attention will continue for some time. The spate of interest is due to a series of coincidences: a powerful House of Representatives subcommittee held hearings after its chairman learned about the IRB system during a previous session on research in underdeveloped communities; the Department of Health and Human Services's Inspector General (DHHS-IG) released a report on IRBs; the National Institutes of Health (NIH) Office of Extramural Research completed a report on clinical trial monitoring; the National Bioethics Advisory Commission (NBAC) readied a report on research involving persons with mental disorders; the states of Maryland and New York completed studies of research with subjects who lack decision-making capacity; and advocacy groups protested a psychiatric research project involving inner city children.

**Comments**
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**Bioethics Inside the Beltway**

# *IRBs Under the Microscope*

Jonathan D. Moreno

The spring and summer of 1998 were seasons in the sun for institutional review board (IRB) aficionados. Rarely have the arcana of the local human subjects review panels been treated to so much attention in both the executive and the legislative branches of government, not only at the federal but also at the state level. And it looks as if the attention will continue for some time. The spate of interest is due to a series of coincidences: a powerful House of Representatives subcommittee held hearings after its chairman learned about the IRB system during a previous session on research in underdeveloped communities; the Department of Health and Human Services's Inspector General (DHHS-IG) released a report on IRBs; the National Institutes of Health (NIH) Office of Extramural Research completed a report on clinical trial monitoring; the National Bioethics Advisory Commission (NBAC) readied a report on research involving persons with mental disorders; the states of Maryland and New York completed studies of research with subjects who lack decision-making capacity; and advocacy groups protested a psychiatric research project involving inner city children.

Underlying these proximate causes for the IRB blitz is a growing realization that the already considerable clinical trial enterprise will expand significantly over the next few years. Congress is talking about giving the politically popular NIH half again the budget it currently receives, which in turn will stimulate more commercially supported research. The director of the National Cancer Institute is considering a five-fold increase in the number of subjects enrolled in oncology studies over the next several years. Phase I cancer studies are among the most ethically sensitive, so IRBs will have more work cut out for them if this goal is reached. Adding to the rush of interest in IRBs are the government's recent apology to the survivors of the syphilis study in Tuskegee, continuing congressional dissatisfaction with the way the Pentagon handled its vaccine distribution during the Gulf War, and the controversy about AZT trials in developing countries.

## On the Hill

Congressman Christopher Shays, the moderate Connecticut Republican who has developed an interest in human research issues, convened hearings on human subjects research and the IRB system on 11 June 1998. Shays chairs the House Government Reform/Human Resources Subcommittee. The committee's ranking minority member is Edolphus Towns of Brooklyn, NY, who shares Shays's interest in this area.

The immediate rationale for the hearings was the release that day of the DHHS-IG report, *Institutional Review Boards: A Time for Reform*. The subtitle was changed from *A System in Jeopardy* apparently after some people in DHHS expressed reservations about its seemingly alarmist tone, but the IG staffers who testified before Shays's subcommittee insisted that they stood behind the message that the IRB system is in trouble if considerable reforms are not undertaken. Among the factors in the research environment cited as support for the bleak forecast: managed care, commercialization, multi-site trials, high IRB workloads, minimal IRB oversight of approved studies, conflicts of interest, insufficient training of IRB members and investigators, and lack of IRB self-studies (DHHS-IG 1998).

As is normally the case for congressional oversight hearings, the first panel of witnesses consisted of executive branch officials, including Eric Meslin, Executive Director of the National Bioethics Advisory Commission, and Gary Ellis, Director of the Office for Protection from Research Risks (OPRR). Shays pressed Ellis on the extent to which OPRR conducts on-site investigations of complaints about abuse of human subjects. Admitting that on-site investigations are rare, Ellis suggested that the agency is inadequately staffed to follow up on complaints as quickly as it might wish. The members of Congress who were present at the hearings generally expressed concern about the DHHS-IG's findings.

The second panel that day, which Shays was unable to attend, set a different tone. Four of the panelists--Paul Appelbaum of the University of Massachusetts at Worcester, Robert Levine of Yale University, Angela Bowen of the Western IRB (a private clinical trials review firm), and I--were invited as authorities on the current condition of the IRB system. Bert Spilker of PhRma (Pharmaceutical Research and Manufacturers of America) gave the industry view. All of us generally conveyed the same message: that the local review principle on which the current system is founded is still the right one; that the system needs to be improved because of changes in the way clinical studies are conducted; and that although the system is in need of improvement, it is not in danger of imminent collapse.

Two other panelists--Timothy Walsh and John Oldham, both of the New York Psychiatric Institute and Columbia University--were, in effect, invited to defend a fenfluramine challenge study. The study, which aimed to examine the relationship between serotonin levels in the brain and aggressive behavior, involved younger siblings of boys who had been in the New York Family Court system. Congressman Towns expressed outrage that the study apparently deliberately excluded white subjects, but Walsh responded that the documents only seemed to allow that exclusion, and that in fact the IRB involved had instructed the investigators that they could not arbitrarily exclude results concerning white children from their data. What started as a great debate on racially charged research ended as a colloquy on research documentation. Nevertheless, Congressman Towns has not let the matter drop.

## The Road to Reform?

The DHHS-IG report that theoretically occasioned the Shays hearings is organized in four separate documents: one, the "Overview and Recommendations," and three others on various aspects of the current status of IRBs, "Their Role in Overseeing Approved Research," "The Emergence of Independent Boards," and "Promising Approaches."

The recommendations include several that would reform federal requirements so that IRBs would have more flexibility but also more accountability. To strengthen IRB oversight the DHHS-IG report suggests mandating Data Safety Monitoring Boards (DSMBs) for multi-site trials. The Food and Drug Administration would be required to inform IRBs about any sanctions against investigators, and research sponsors and investigators would have to inform them about prior IRB review of a research plan. The report recommends that IRB members increase their awareness of actual research practices by visiting study sites. Although, as the report notes, such visits would represent a departure from the historic relationship between IRBs and investigators, IRBs already have the authority to conduct active monitoring, though in practice it is rarely done.

The report also recommends that both investigators and IRB members receive training in research ethics. To this end, it urges that the Public Health Service require all of its grantee institutions to have programs to train investigators in human subjects protections, similar to the current NIH requirement for trainees. Investigators would be required to attest in writing that they are familiar with and will uphold federal subject protection policies, and institutions would have to certify that they provide a continuing education program for IRB members. There are also recommendations concerning conflicts of interest, workload pressures on IRBs, and the need to strengthen the federal capacity to deal with IRB performance problems as they arise.

The DHHS-IG report notes the increase in independent or private IRBs, which are created outside of the institutions that conduct research, in order to satisfy federal requirements for board review of clinical research proposals. Although these boards are often more efficient than traditional research-center-based IRBs, they are not the local review bodies envisioned in previous understandings of human subjects protections. Independent IRBs also are alleged to contribute to conflict of interest concerns and worries about the potential for "IRB shopping," in which sponsors go from one board to another until one approves their study.

To signal that many IRBs are taking the lead in responding to changes in their environment, the report notes a number of promising approaches. To manage their growing workload, some IRBs are creating multiple boards or increasing the number of meetings. Some institutions have begun to require investigators to attend training programs. One IRB uses a research intermediary to check on consent processes with each psychiatric patient in a study. Some IRBs devote part of each meeting to education, and at least one has developed a special liaison program to reach out to the ethnically diverse community from which the subjects of the protocols it reviews are recruited. Another IRB has created a self-evaluation process.

The ultimate impact of the DHHS-IG report on IRBs will be hard to disentangle from the effect of some other forces currently at play. On 24 June 1998, about two weeks after the Shays hearings, Congressman Towns introduced a bill intended "to increase oversight protection for children and mentally disabled individuals who participate in clinical research trials." In his remarks introducing the bill on the House floor, Towns cited the DHHS-IG report and a previous General Accounting Office report, both of which express reservations about the extent to which the current IRB system could fulfill its mission. Towns's bill would require "that any IRB that uses children or mentally disabled individuals in research must report to the Secretary of Health and Human Services concerning the participants, the nature, objectives and reasons for the research and the source of funding. The Secretary will be required to make this information available to the public." Among the bill's bipartisan group of powerful co-sponsors is Shays, his fellow Republican, Dan Burton of Indiana, and Democrat Henry Waxman of California.

Towns's bill relies on publicity rather than on specific new requirements to be applied to IRBs. By contrast, the National Bioethics Advisory Commission, in its draft report on research involving persons with mental disorders, requires that IRBs reviewing such proposals have two members familiar with the concerns of persons with mental disorders in research. NBAC also calls on IRBs to look for specific elements of protocols before granting approval to clinical studies with this population. For example, a psychiatrist not involved in the research would be responsible for assessing the capacity of potential subjects to give informed consent.

The coincidence of the DHHS-IG report, the proposed NBAC recommendations, and the Towns bill does not necessarily mean that comprehensive, "top down" reform of the IRB system is in the offing, at least not if the Common Rule--the research regulations to which no less than 17 federal agencies are supposed to comply, although actual compliance patterns are in dispute--is to be the vehicle. Since inclusive reform would require rule changes in all of the agencies, and since it took 10 years for the agencies to adopt the Common Rule in the first place, one can expect the pace of amendments to be glacial. Somewhat more likely for the present is the alteration of at least the DHHS rules, which cover Public Health Service grants. Still more feasible is the prospect that many IRBs will undertake their own reform efforts.

## Just the Facts

Much of the information about the IRB system, including that used to form the basis of many of the recent reports, is impressionistic. Even the much touted DHHS-IG report seems to be founded on little original research: "interviews and group discussions with representatives of 75 IRBs," "attendance at IRB board meetings," and "site visits to six IRBs based in academic health centers" are among the methodologies listed in the report. Secondary sources include federal records and previously published reports, articles, and books.

The dearth of hard data about the IRB system should improve with a report commissioned by the NIH Office of Extramural Research, a review draft of which was released on 19 May 1998. Among the most impressive results of the survey is a picture of the overall IRB workload in a recent year: 284,000 reviews, including 105,000 initial reviews; 116,000 continuing/annual reviews; and 63,000 reviews of amendments to approved protocols. Of special importance is the finding that the IRBs that review the highest volume of protocols, about 10 percent, account for 37 percent of the national total of completed reviews, and the 246 high-volume boards account for 85 percent of the total. Another finding is that the high-volume IRBs have a higher approval rate than low-volume IRBs, 69 percent as compared to 55 percent. Concerning vulnerable subjects, more than one-fifth of investigators said their subjects had serious conditions, and 16 percent of all protocols included subjects with a terminal condition, a medical emergency, or "attenuated ability to comprehend" (NIH Office of Extramural Research 1998).

The survey results presented in the NIH draft report suggest that IRB function could be much improved by focusing attention on the higher-volume boards. Specific innovations, including some along lines suggested by the DHHS-IG report, might involve splitting a board or establishing more than one IRB at an institution, aided by increased professional staff. Such "unglamorous" changes could be far faster and more effective than waiting for federal rules to be amended or overhauled.

## Incremental Change

Adjusting IRB membership is a popular partial solution to complaints about research involving persons with impaired decision-making capacity. Early in 1998, a special NIH panel composed of investigators and others familiar with IRB issues filed its report *Research Involving Individuals with Questionable Capacity to Consent*. The panel recommended that IRBs "include *at least one* voting member with the background, experience, and willingness to act as a representative of such subjects, independent of the research and investigators" (emphasis in original). Other IRB personnel might have a role as well, especially when risks are greater than minimal and potential subjects have questionable capacity to consent. In such cases, "IRBs should discuss and document the potential value of an independent monitor." Family members or legally authorized representatives could also be identified as part of the consent process when the subjects have questionable capacity to make research decisions (NIH 1998).

Although the panel's substantive suggestions appear to be similar to those of the NBAC draft report, the NIH report exhibits far less enthusiasm for the possibility of new or additional regulations. The NIH report emphasizes that IRBs already have the authority to put the panel's recommendations into place, while the draft NBAC report looks to changes in the regulatory framework. The NIH report also calls on state governments to create statutes recognizing close family members as appropriate legally authorized representatives for persons with mental disorders who lack decision-making capacity for certain kinds of research.

## States' Rights

Meanwhile, Maryland and New York have been pursuing related research policy issues in task forces convened by state governmental authorities. Maryland pioneered these deliberations when its attorney general established a Workgroup on Research Involving Decisionally Incapacitated Subjects that met frequently for two and a half years. It is perhaps no accident that Maryland led the nation in deliberating on the subject, given that NIH voluntarily adopts Maryland law regulating medical care and research, and much relevant research is conducted on its sprawling Bethesda, Maryland, campus.

The Maryland workgroup's strategy was to develop a proposed statute to cover all research in the state involving decisionally incapacitated individuals, including research covered by the federal Common Rule, thus asserting Maryland's jurisdiction over all research conducted within its borders. Although the group's report mainly relates to capacity assessment and advance directives, it also requires investigators to disclose any previous IRB decisions to the board now considering their proposal (to discourage IRB shopping). The group pays close attention to studies that involve the withdrawal of standard medication, a frequent practice in studies conducted with subjects who have schizophrenia. In such cases, the IRB would appoint a "medically responsible clinician" who is independent of the research and would counsel the legally authorized representative of the subject if the latter's continued involvement in the study becomes medically inadvisable (Workgroup on Research Involving Decisionally Incapacitated Subjects 1998). This role for an independent clinician is similar to that proposed by NBAC.

In New York, an Advisory Work Group on Human Subject Research Involving the Protected Classes, appointed by the health commissioner and chaired by Columbia University psychiatrist Herbert Pardes, was convened following the extensive publicity from a lawsuit brought against the state by former patients in one of its facilities, the New York Psychiatric Institute. The plaintiffs charged that human subjects protections for persons with mental disorders in state facilities were inadequate. Although a lower court found for the plaintiffs, including a finding that the state had violated constitutional rights, the state's highest court voided that analysis, simply allowing to stand the conclusion that the health department had not established its policies through an adequate process (*T.D. v. New York State Office of Mental Health*, 650 N.Y.S.2d 173, 193-94 (N.Y. App. Div. 1996), *appeal dismissed by* 680 N.E.2d. (N.Y. 1997); *leave to appeal granted by* 684 N.E.2d 281 (N.Y. 1997); *and appeal dismissed by* 1997 WL 785461 (N.Y. Dec. 22, 1997)).

The New York workgroup's report, *Recommendations on the Oversight of Human Subject Research Involving the Protected Classes*, approves of the basic IRB system but calls on the state's health department to provide training and technical assistance to IRBs. It also suggests a registry of IRBs and IRB-approved research. There are several suggested requirements for the boards themselves, including documenting the risk-benefit category into which a study falls, designating an independent consent monitor for studies that present more than a minor increase over minimal risk and no direct benefit to

decisionally incapacitated subjects, and involving at least one family member and one recipient of mental health care in the review and approval of studies involving decisionally incapacitated persons (Advisory Work Group 1998).

The New York State Commissioner of Health appointed another workgroup, the Workgroup on IRB Guidelines, chaired by Nancy Dubler of Montefiore Medical Center in the Bronx, to focus on research with healthy volunteers. This panel was established following the tragic death of a University of Rochester undergraduate after an invasive procedure with an anesthetic agent that proved to be an overdose for this young woman, who was to have been paid $150 for participating in the study. The group filed its "Final Draft" report early this summer after meeting for about a year. The report echoes a recurring theme and urges increased IRB monitoring of studies. IRBs should pay closer attention to risks posed by research, especially when there is no direct benefit to the subject, and they should be more aware of recruitment issues, including the potential for investigators to have conflicts of interest when recruiting their own patients for research in which they are involved (Workgroup on IRB Guidelines 1998).

If there is a recommendation conspicuous by its absence from most of these documents, it is the lack of support for a "super" or "national" IRB. A research group I chaired at the University of Pennsylvania Center for Bioethics called for national review for particularly sensitive research (Moreno and Caplan 1998). However, most of the sentiment seems to be reformist rather than revolutionary, with local IRBs bearing the brunt of greater responsibility. Several reports call for universities to allocate more resources to the support of their local board(s), including appeals for more educational opportunities for IRB members and investigators.

A problem with improving the IRB system is that, although the inadequacies of the current system are not under dispute among those familiar with it, nobody really knows what would be better. Local review does allow for familiarity with local conditions that could be relevant to human subjects research, and it provides a convenient source of cheap labor in the form of professors who feel obliged to serve. But as a self-policing system, it invites charges of cronyism, and localism can be an obstacle to moral consistency. But, given the American preference for decentralization, change is likely to be facility-based and incremental.

## Trouble in Baltimore

Just as all these committees and commissions and research groups reported on the limitations of the IRB system, and some on the involvement of persons with decisional impairments in research, the federal Office for Protection from Research Risks completed a review of the Maryland Psychiatric Research Center (MPRC). Responding to complaints made to NBAC about human subjects protections at the facility, which is affiliated with the University of Maryland medical school, OPRR conducted a three-day investigation. It found that some of the informed consent documents did not meet DHHS regulations. The OPRR's "decision letter" to the medical school's dean required that MPRC review its consent documents for all active protocols. It also required that the

university provide education to IRB members concerning special protections for vulnerable populations and determine that protections for these populations had been satisfied in research protocols, as required under federal regulations but not always implemented by MPRC (letter from Susan Crandell, OPRR, to Donald E. Wilson, M.D., Dean of the Medical School, University of Maryland, Baltimore, 16 April 1998).

Along with a number of other requirements concerning its IRB's practices, MPRC joined the New York Psychiatric Institute as a state institution whose human subjects protections have come under intense public scrutiny. Now that some inadequacies have been identified, it seems unlikely that the scrutiny will end soon. Whether by legislation or other pressures, new constraints will almost certainly be imposed on psychiatric research, especially with regard to certain controversial study designs, such as those involving "drug holidays," in which patients are removed from their established drug regimens. IRBs also will be encouraged to accept expanded responsibilities and in many instances to tighten their procedures. An interesting spectacle in the coming months and years will be the response of major research institutions to these new pressures on their prestigious and lucrative clinical research programs.

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