Ethical and Policy Issues in Research Involving Human Participants

Volume II
AN EXAMINATION OF ISSUES PRESENTED BY PROPOSALS TO UNIFY AND EXPAND FEDERAL OVERSIGHT OF HUMAN SUBJECT RESEARCH

Commissioned Paper
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Executive Summary

The National Bioethics Advisory Commission (NBAC) seeks to determine whether to improve the federal regulatory system for the protection of human subjects, and if needed, in what ways. This paper was commissioned to examine whether NBAC should recommend unifying federal oversight of federal and private human subjects research under a single government office such as the Office for Protection from Research Risks (OPRR).

The question posed by NBAC encompasses two related but distinct groups of issues: 1) those pertaining to unification of federal human subject protection oversight in a single agency or office and 2) those raised by expansion of the scope of federal oversight to cover not just federally funded, but also privately conducted human subjects research.

NBAC seeks to protect all human subjects of research against abuse or exploitation. But to get to that goal, NBAC must grapple with several fundamental questions: should citizenship or residency in the United States ensure a minimum level of protection against the risks inherent in research involving human subjects? If so, how is that level of protection defined? Is it possible to provide that level of protection efficiently, cost-effectively, and without burdening research that presents little or no risk to human subjects?

Our current system for protecting human subjects of research has many acknowledged strengths, and it balances effectively the competing interests always present in a regulatory system. It has served remarkably well for decades, and achieved many of the goals it was originally designed to meet. On the other hand, aspects of the system have known deficiencies that require correction and improvement. The recommendations in this paper are not designed to detract from the strengths of a good system, but to improve upon it in ways that will be beneficial without undue regulatory burden.

This paper recommends four elements for an improved regulatory system:

1. Correcting structural/organizational deficiencies in the present regulatory system,

2. Unifying federal oversight of human subject research in one federal office or agency, but leaving in place the current jurisdiction of FDA over the approval of drugs, medical devices, and biologics,

3. Using existing federal offices as structural models for unified oversight of human subjects research, and

4. Expanding the scope of regulation incrementally rather than globally. This recommendation envisions an expansion of federal jurisdiction only to identified categories of research that meet the criterion of presenting known risks to human subjects of research.

Correcting Deficiencies. A series of studies over recent years, culminating in the June 1998 Department of Health and Human Services (DHHS) Office of the Inspector General (OIG) report on Institutional Review Boards (IRBs) and the NBAC-commissioned papers by Drs. John C. Fletcher and Charles R. McCarthy, have identified deficiencies in our present system for protecting human subjects. These must be corrected in tandem with any expansion of federal oversight. Of particular concern are the conflicts of interest inherent in OPRR's location within an agency for which it has a monitoring responsibility. Other key issues include the inadequate (and evidently declining) governmental resources allocated for the protection of human subjects; inconsistency of human subject protection across the government; and minimizing bureaucratic procedures in favor of educational efforts and true accountability.

Unification of Oversight Responsibilities. Responsibility for oversight of federally conducted or sponsored research should be consolidated into one federal agency or office. Responsibility for drug, device, and biologic approvals should remain with FDA, but the two agencies should develop a memorandum of understanding to codify their cooperation and coordination. Information is presented on existing governmental agencies that might serve as models for a reorganized and strengthened human subject protection office.
Recommended Strategy for Expanding Regulatory Scope. This paper proposes adopting a strategy of including all research posing “known risks” to human subjects of research under federal jurisdiction regardless of the source of funding or nature of the organization conducting the research. This approach is sensitive to current societal concerns about unchecked governmental regulation and should fare well under cost/benefit analyses. If NBAC adopts this proposed strategy, further work will be necessary, first to devise a mechanism for defining known risks, and then to develop a procedure for bringing relevant categories of research under federal jurisdiction.

I. Introduction

NBAC unanimously adopted a resolution on May 17, 1997, that “No person in the United States should be enrolled in research without the twin protections of informed consent by an authorized person and independent review of the risks and benefits of the research.” This position was reinforced when President Clinton asserted in a commencement address that same month that “[w]e must never allow our citizens to be unwitting guinea pigs in scientific experiments that put them at risk without their consent and full knowledge.” While the NBAC resolution and presidential declaration seem to be straightforward expressions of fundamental American beliefs about human rights and dignity, translating them into practice will be far from straightforward.

First, whether or not it is immediately apparent, these statements imply a sweeping expansion of federal regulation of research involving human subjects. Paradoxically, cats, dogs, rabbits, hamsters, guinea pigs, and nonhuman primates have more federal protection from the risks of participation in research than do humans. The federal government has regulated all research on these animals—regardless of the source of funding—since the Animal Welfare Act was first enacted in 1966. In contrast, the only research involving human subjects that is regulated by our government is that which a) is funded by one of seventeen federal agencies, b) is conducted without federal funds at an institution voluntarily extending federal oversight to the research, or c) involves drugs, devices, or biologics falling within the jurisdiction of the FDA. Absent these conditions, individuals with concerns or complaints about their treatment have no recourse except through civil litigation or criminal statutes. Thus at present, the minimum protections NBAC and the President seek are not even provided in all research conducted or paid for by the federal government, let alone that performed in the private sector.

While we cannot know how much unregulated research on human subjects takes place in the United States—precisely because it is not regulated—indications are that it is significant. Information about problematic practices in such research surfaces with sufficient regularity that expanded government oversight must be seriously considered.

Second, our system for the protection of human subjects of research is more than 30 years old, and, while the basic system is sound, we know that it has shortcomings. Beyond our knowledge of the existence of problematic unregulated research, we know that even regulated research may be exposing human subjects of research to inappropriate risks. Some of the deficiencies in the current regulatory structure and implementation are described in the Report of the DHHS Inspector General, Institutional Review Boards: A Time for Reform (June 1998), the Report of the Human Radiation Interagency Working Group (March 1997), the General Accounting Office (GAO) Report, Scientific Research: Continued Vigilance Critical to Protecting Human Subjects (1996), and the findings of the Advisory Committee on Human Radiation Experiments (ACHRE) (October 1995). To implement fully the NBAC resolution and give meaning to the President’s declaration, some of the identified problems in the current system must be corrected.

A pivotal issue is how federal oversight in our purposefully decentralized system of oversight for human subjects is fractionated, with 17 separate federal agencies holding responsibility. The decision to place primary responsibility for human subject protections with local IRBs at institutions conducting research is well suited in
many respects to our thriving research system. But federal oversight and protections are unevenly implemented and variably enforced, leading to serious gaps in human subject protections.

Another issue that NBAC must confront directly is the federal commitment to human subject protection as revealed through the resources devoted to the task. There is evidence that funding in this area has declined despite significant increases in research. Unless accompanied by adequate resources, neither reforms of our existing system nor expansion of federal protection will produce meaningful or long-lasting change.

Any proposal for change should be grounded in a clear statement of principles and goals: What is to be accomplished? The NBAC resolution already contains two goals: informed consent and independent ethical review for all persons “enrolled in research.” But the resolution does not define the “research” it intends to encompass or the level of risk at which these twin protections should attach.

Comprehensive application of the present federal definition of research—purposefully designed to be broad in its application and reach—could sweep myriad low-risk activities into a regulatory structure with unknown costs and implications. Activities that have never before been labeled as “research” could become subject to regulation, commanding resources for their review and oversight, ultimately to the detriment of human subjects in higher risk situations.

Many of this nation’s 3,000-plus IRBs are already overloaded by their current workloads. As the GAO report observes:

IRB reviews are labor intensive and time consuming, forcing boards to balance the need to make reviews thorough against the need to get them done. IRB members...are not paid for their IRB service. Board members themselves...face a heavy workload and others in the research community have raised concerns that heavy workload impairs IRB review.

Research institutions would complain—and with some merit—if their workload is increased by a broad expansion of types of research requiring IRB review. One result could be a dramatic increase in the number of for-profit IRBs, or an incentive for IRBs to provide superficial reviews, or both. Careful design and implementation will be required to avoid a system that substitutes mechanical review for substantive ethical considerations.

Expanding federal jurisdiction to assure that "no person" is enrolled in research without the twin protections specified by NBAC requires care and focus—and will require changes in federal law and the commitment of additional federal resources to assure compliance with that law. To explore the issues raised by a unification of oversight into one federal agency and by a proposed expansion of federal oversight of research involving human subjects, we must examine 1) the present structure of federal regulatory protection, including its functioning, shortcomings, and the gaps in its coverage and 2) practical problems inherent in expanding the scope of federal oversight. These two issues are intertwined to a considerable degree.

II. The Present Federal System for Human Subject Protection

Government regulation frequently arises as a reaction to revelations that disturb the public conscience. The federal oversight of research involving human subjects is no exception. As recounted in David J. Rothman’s Strangers at the Bedside: A History of How Law and Bioethics Transformed Medical Decision-Making, the entry of the federal government into this realm was driven by a combination of dramatic scientific/medical advances and scandals concerning abuses of human subjects of research. Medical advances in genetic engineering and heart transplantation gave rise to questions about the beginning, end, and quality of life. At the same time, disclosure of the now infamous Tuskegee experiment in 1972 and the abuses of human subjects detailed in Dr. Henry Beecher’s 1966 paper in the New England Journal of Medicine drew attention from the media and Congress. These in turn opened new areas of ethical debate including whether certain procedures should be governed outside the physician-patient relationship. More sophisticated versions of these questions are still with us today.
The reaction of the biomedical research establishment to these questions and to the prospect of government intrusion into the historical preserve of physicians and researchers was negative and strong—but not sufficient to convince Congress that patients and human subjects of research would be adequately protected without government intervention. Nonetheless, the strength of the reaction helped to shape the system of protection that resulted; similarly strong reactions can be expected to new proposals for change.

A. Background and Overview

Before moving to expand federal protections to subjects of currently unregulated research, we should examine the present system, which has grown incrementally over a period of years. The first federal policies covering research funded by the Department of Health, Education and Welfare (now DHHS) were issued in 1966. The first congressionally mandated commission, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission), started its work in 1974. It produced ten reports over four years that provide the ethical foundation for the system of protections in place today. Even so, it took until 1991 for a subset of federal agencies to agree upon the Federal Policy for the Protection of Human Subjects as the core regulation governing research conducted by or under the auspices of the government. This policy is often referred to as “the Common Rule.” The Common Rule is not followed by all federal agencies, and it is unevenly enforced by those that do.

In 1994, Dr. Robyn Y. Nishimi of the Office of Technology Assessment (OTA), testified before Congress that:

No statute...governs the general oversight of research involving Americans. Moreover, the current system, while changing incrementally, has fallen short of implementing, or did not implement at all, recommendations made between 1973 and 1982 by an ad hoc committee of DHEW, a congressional report and two congressionally mandated commissions.

Research involving human subjects may be regulated by the federal government through three separate mechanisms: a) because it is sponsored by a federal office or agency subscribing to the Common Rule; b) because an institution conducting research not sponsored by the federal government has voluntarily granted jurisdiction over the research to OPRR through a negotiated assurance; or c) because the research involves regulated drugs or medical devices over which the FDA has jurisdiction. An unknown quantity of research is not regulated either because the sponsoring/conducting agency does not subscribe to the Common Rule or has not negotiated an assurance extending federal jurisdiction or because the research is privately sponsored/conducted and not subject to FDA approval.

1. The Common Rule

Summary of Common Rule Provisions. The approach of the Common Rule to regulation of human subject research is decentralized, involving negotiation of assurances by the institutions where research is conducted with federal agencies certifying that certain procedural and substantive protections will be provided. While these assurances are received and overseen by the various federal agencies, review of specific proposed experimental protocols and informed consent forms occurs at the local level through IRBs. Federal requirements govern the composition and activities of IRBs, but as we shall see, true oversight and accountability for the rigor and consistency of IRBs has not been attained.

Six categories of research are exempt from full IRB review under the Common Rule. These review procedures permit research meeting specific, narrow criteria to proceed without any formal review. The six exemption categories, developed with public comment and through negotiation and policy formulation involving an interagency committee over a period of ten years, offer important insight into one mechanism that might be employed to address the practical problems that could arise from broadening the scope of federal regulation. (See below.) There are additional categories of research for which IRBs may use expedited review procedures,
on the theory that the types of research involved, like voice recordings or collection of fingernail clippings, are less intrusive and pose a low level of risk to the subject.\textsuperscript{14}

**Application of the Common Rule.** Seventeen federal agencies that fund or conduct research subscribe to the Common Rule and thus use an approach similar to that of DHHS, the lead federal agency in this area, with the important exception that most do not have an active program for assuring compliance with applicable regulations. While there is no definitive assessment of how many federal agencies conduct or fund research on human subjects, the 1981 report of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Protecting Human Subjects*, documented that 23 federal entities funded research involving human subjects.\textsuperscript{15}

Dr. Nishimi of OTA testified to Congress in 1994 that:

\begin{quote}
...a definitive picture of current federal implementation and oversight of existing regulations to protect human research subjects is not available....Currently, information from all agencies on the total number of all research grants or contracts, total funding for research and grants involving human subjects, and number of full time equivalent personnel devoted to assurance and compliance has not been collected in a coordinated or centralized fashion....

For some agencies, information even limited to the number of, funding levels for, and types of research involved for current grants or contracts using human subjects could not be reported as recently as March 1994, although the common rule has been effective since June 1991. Without such information, ensuring that proper institutional assurances are in place and then overseeing compliance would appear to be problematic.\textsuperscript{16}
\end{quote}

Within DHHS, OPRR assumes oversight responsibility for both human and animal subjects of research. The FDA also has responsibility for protecting the rights and welfare of human subjects of research, in the context of its required approvals for drugs and medical devices. While both OPRR and FDA have mechanisms for reviewing cases of alleged noncompliance with federal regulations and responding to them,\textsuperscript{17} most other agencies do not. As Dr. Nishimi noted in 1994:

\begin{quote}
...agencies will not be aware of violations of existing regulations unless a rigorous system is in place to monitor compliance. Put another way, those Departments and agencies that are not looking for problems will not find any problems.\textsuperscript{18}
\end{quote}

The ACHRE inventoried federal experiments on human subjects and found that:

\begin{quote}
In most federal agencies, current mechanisms of oversight of research involving human subjects are limited to audits for cause and a review of paperwork requirements. These strategies do not provide a sufficient basis for assuring that the present system is working properly.\textsuperscript{19}
\end{quote}

**2. OPRR Oversight System**

OPRR relies heavily upon the assurances it negotiates with institutions conducting research. These assurances contain the institutions' provisions for protecting the welfare of human subjects and generally follow common patterns. In addition to the promises institutions provide in their negotiated assurances, OPRR provides educational support and information to IRBs and queries institutions about reports of noncompliance. OPRR conducts a number of record reviews through paper correspondence and a much smaller number of on-site, for-cause reviews of IRB effectiveness. Both the GAO and the DHHS OIG compliment the effectiveness of OPRR's compliance reviews, but both also comment upon the extraordinarily limited extent of on-site visits, due to staffing and budgetary constraints.
Currently, OPRR negotiates an assurance with each institution that receives research support from DHHS. Each assurance requires significant amounts of time and review by OPRR. According to the GAO, in 1996 OPRR had about 14 full-time equivalent staff devoted to human subject protection, with a budget for those activities of under $1 million. OPRR augments its professional staff with three physician volunteers.

Most major institutions accepting federal research funding negotiate Multi Proj ect Assurances (MPAs) with OPRR through which they agree to provide the same protections to all subjects of research conducted at the institution that they do for research funded by DHHS. There are almost 450 MPAs covering more than 750 entities operating around 700 IRBs; they are virtually all in the United States. Two to four times as many institutions negotiate only Single Project Assurances (SPAs) for each individual project funded in whole or in part by DHHS (covering around 3,000 IRBs), or Cooperative Project Assurances (for multisite clinical trials), with another 1,250 associated IRBs.

There are about 3,000 active SPAs—locations where we know that some DHHS-regulated research is conducted but no MPA is in place to cover other research that may be performed at that institution. At these institutions, other research involving human subjects may occur without any governmental provided protections for the subjects of that research. This does not necessarily mean that the research is not reviewed by an IRB, as institutions may choose voluntarily to extend those protections to all subjects of research—or they may not. It does mean that there is no federal jurisdiction to investigate if a subject of research files a complaint.

OPRR reports that negotiation of assurances for SPAs requires more time than other negotiations, because they usually involve OPRR scrutiny of protocols and informed consent documents from institutions with little or no history of review of research involving human subjects. Because DHHS funds research in 80 countries around the world, institutions negotiating SPAs are not all in the United States.

These and other recent reviews of the IRB system emphasize the changes that time and resource constraints have brought to their oversight by OPRR. While all contribute to a conclusion that OPRR does a good job of protecting human subjects of research, they also illustrate that its resources are inadequate for its present responsibilities and indicate areas where changes could strengthen its performance.

The assurance negotiation process, for example, has by most accounts become routinized. The NBAC-commissioned paper by Dr. McCarthy provides background on the educational nature of the assurance negotiation process in its early phases: He implies that these negotiations were usually conducted on-site at institutions and describes how mutually beneficial these exchanges were, both for institutions with little background in these issues and for OPRR officials in gaining insight into the institutions culture. By now, the negotiation process has lost much of this educational flavor; perhaps its time has just passed.

The McCarthy paper also describes an OPRR that was able to sustain a much larger educational program than is now the case. As an ongoing constant educational program is essential if consistency is to be achieved in a decentralized system, this is a serious matter. It is not an overstatement to suggest that, in a large distributed oversight system, high-quality educational programs are the cornerstone of true accountability. The report of the ACHRE went so far as to recommend that:

...efforts be undertaken on a national scale to ensure the centrality of ethics in the conduct of scientists whose research involves human subjects....The necessary changes are unlikely to occur solely through the strengthening of federal rules and regulations or the development of harsher penalties....The federal government must work in concert with the biomedical research community to exert leadership that alters the way in which research with human subjects is conceived and conducted so that no one in the scientific community should be able to say "I didn't know" or "nobody told me" about the substance or importance of research ethics.
Much of OPRR's ability to conduct such programs has since been curtailed by budgetary reductions and limitations, although an ongoing set of programs is offered annually through co-sponsorship arrangements. Dr. McCarthy raises cautions against the conflicts of interest that can arise when regulated institutions are assuming responsibility for part of the cost of educational programs in this way.

OPRR's reliance upon a paper-based and time-intensive assurance negotiation system is no longer desirable. OPRR agrees with the calls from external observers that it is time to make changes in the negotiation of assurances.\(^{27}\) Replacing the assurance system with a streamlined registration system seems a sound alternative. If change of this nature were adopted expeditiously, it would free some resources for activities more conducive to true accountability. OPRR should be able to make this change without regulatory modification, but should be encouraged to do so by NBAC.

Other recommendations of the OIG—several of which mirror changes OPRR staff have indicated they would like to adopt—will require more resources than are presently available to OPRR. This is a central issue with which NBAC must grapple as it formulates it recommendations.

3. FDA Oversight System
The FDA is responsible for the safety and effectiveness of medicines and medical devices. As part of its regulatory responsibilities, FDA requires that studies involving investigational new drugs, devices, and biologics receive review and approval by an approved IRB and that researchers submit statements that they will uphold ethical standards. FDA has “concurred” with the Common Rule, but has not adopted it in its entirety; while its regulations are largely congruent with those that OPRR enforces, there are differences in its IRB and informed consent regulations.

A major difference is that FDA does not require or negotiate assurances with institutions. It oversees IRBs through an inspection program, in which it routinely performs on-site procedural reviews of IRBs to determine whether they are in compliance with their own procedures and with applicable FDA regulations. The GAO reported that FDA employed about 13 full-time equivalent staff members devoted to IRB inspections in fiscal year 1995.\(^{28}\) FDA also has monitoring activities for individual drug studies and for clinical trials. Each involves reviewing compliance with consent requirements and other human subject protection protocols.

The GAO reviews concluded that while the FDA program is rigorous and that it detects (and corrects) problems in human subject research, “FDA's inspection program is geared more toward protecting the eventual consumer of the drug than the subjects on whom the drug was tested.”\(^{29}\) If NBAC wishes to assure protection for human research subjects, this observation should trigger serious examination and consideration.

4. Nonsubscribing Federal Agencies
Subjects of research conducted or funded by federal agencies that do not subscribe to the Common Rule do not receive its core protections. There are indications that research is funded or conducted by the Nuclear Regulatory Commission, the National Endowment for the Humanities, and the Department of Labor.\(^{30}\)

In 1995, the ACHRE found that the magnitude of research conducted by federal agencies not in compliance with the Common Rule is a significant concern and recommended that there be an assessment of the level of that research. It further recommended action to “ensure that all subjects are afforded the protections it offers.”\(^{31}\) Anticipating the ACHRE findings, President Clinton issued an Executive Memorandum in 1994 intended to address gaps in government coverage; specifically, he ordered that all federal agencies and departments should come into compliance with the Common Rule and to suspend noncompliant experiments immediately.\(^{32}\) There is no evidence that any department or agency suspended a single activity following the President's instruction. The staff of NBAC is researching the issue of federal agency compliance with the Common Rule and the Executive Memorandum.
5. A Caveat—Not All Unregulated Research Goes Without Review

It is important to note that federal regulation is neither the only mechanism through which research is independently reviewed nor is it the only way participants in research are offered the protection of informed consent. It may not be appropriate to assume that expanding the scope of federal regulation is the only way to achieve the twin goals of assuring informed consent by subjects and objective review of protocols. Many universities extend to nonfederally funded research the same oversight required by federal regulation, mandating that all research conducted at the institution is subject to review by an IRB. Of course, in virtually all cases this voluntary extension lacks independent compliance oversight, so NBAC must confront the degree to which it considers compliance oversight to be essential to a federal protection system.

B. Documented Shortcomings of the Present System

Two recent reviews, one by the GAO in 1996 and one by the OIG of DHHS in 1998, document serious shortcomings in the functioning of IRBs across the country. Because our decentralized system depends upon local IRBs for review of research protocols, IRBs are the lynchpin of our human subject protection system. The two most recent reports build upon the earlier findings of the ACHRE.

These reports follow a string of earlier reports examining shortcomings in our systems of protections, and containing recommendations that have not been fully implemented. Recall Nishimi's 1994 congressional testimony noting how many recommendations delivered over the decades have not been implemented. In that same testimony, she characterized national responses to problems as fitting a “crisis management” model, in which publicity leads to a commission, but few actual changes. A footnote to her testimony records that the President's Commission made a follow-up report to Congress two years after its first report and called the progress in the interim “disappointing.” Nishimi, in 1994, stated that: “The Commission identified numerous deficiencies in agencies’ mechanisms to protect human subjects. It made a series of recommendations to improve Federal oversight, but to date virtually none has been implemented.”

The ACHRE found in its 1995 report that “in comparison with the practices and policies of the 1940s and 1950s, there have been significant advances in the protection of the rights and interests of human subjects of biomedical research. However, we also find that there is evidence of serious deficiencies in some parts of the current system....“ Their review found evidence of “substantial variation in the performance of institutional review boards” as well as in review of research proposal documents and in informed consent documents. Most importantly for NBAC, the committee found “evidence of confusion over the distinction between research and therapy.”

It is worth remembering that the original National Commission spent a great deal of time in the early 1970s—and commissioned several analyses to assist its deliberations—examining the distinction between research and therapy as it set about devising a recommended definition of “research” to be regulated. ACHRE also articulated concerns about “adult subjects with questionable capacity” and research involving institutionalized children. NBAC is already addressing the concerns ACHRE identified about adult subjects with questionable capacity; the issue of the distinction (if any) between research and therapy will continue to be central to all discussions of appropriate regulatory scope.

Consistent with the comments of other observers, ACHRE recommended that IRBs give more attention to activities that pose more than minimal risk to subjects and that they seek to reduce paperwork and procedural requirements for activities posing less than minimal risk. In other words, focus resources on areas of greatest risk and concern to subjects.

GAO, in its 1996 review of human subject protections, found that “[t]he detection of recent instances of potential or actual harm to subjects both demonstrates that abuses can occur and also suggests that current oversight activities are working...[but] various time, resource and other pressures have reduced or threaten to
reduce the effectiveness of such oversight. GAO found that the heavy workload of IRBs can weaken their oversight; that OPRR's restricted site visit schedule and its location within the National Institutes of Health (NIH) hamper the effectiveness of its oversight of IRBs; and that changes in the nature of research and pressures for availability of unproven medical treatments make it difficult to protect human subjects.

GAO also commented upon the organizational weakness in the location of OPRR within NIH that is examined in the NBAC-commissioned papers by Drs. Fletcher and McCarthy. This is a topic NBAC must address in its final recommendations.

The OIG reports find that "the effectiveness of IRBs is in jeopardy" with six major findings:

1. IRBs face major changes in the research environment, including those stemming from the expansion of managed care, increased commercialization of research, proliferation of multisite trials, new types of research, increased number of research proposals, and the rise of patient consumerism;

2. IRBs review too much, too quickly, with too little expertise;

3. IRBs conduct minimal continuing review of approved research;

4. IRBs face conflicts that threaten their independence;

5. IRBs provide too little training for investigators and board members; and

6. Neither IRBs nor HHS devote much attention to evaluating the effectiveness of IRBs.

While the OIG report found that OPRR's on-site visits provide a better basis for assessment of an IRB's performance than either its assurance process or the FDA inspection process, it also noted that OPRR's resource constraints prevented it from making more than one for-cause site visit in the calendar year between April 1997 and May 1998. The OIG report stressed that it is a cardinal failing of our present system that neither OPRR nor FDA have a primary focus on assuring the effectiveness of IRBs. While the OIG report does not document any widespread abuses, the fact that we have no effective mechanism for assuring the accountability of IRBs is cause for grave concern.

The OIG report recommends "reengineering" the federal oversight process, with specific suggestions for revamping both the OPRR assurance process and the FDA inspection process for IRBs. Several recommendations focus on modifying procedural requirements in order to focus more effectively upon fundamental protections for human subjects of research. This is a theme that NBAC should embrace in all of its recommendations for change.

These findings only reinforce the sense that our existing system requires reform. While these reforms should be included in any recommendations made by NBAC, they should accompany, not supersede, additional changes to address identified risks to human subjects in presently unregulated research.

**Recommendation 1: Correct Identified Deficiencies in Existing Federal Human Subjects Protection System**

Before recommending that the federal government assume expanded responsibility for protection of human subjects involved in research, we should assure that it can fulfill its present obligations appropriately. We know our present review system has defects. Of those issues, the following seem most relevant to the expansion and unification questions posed by NBAC.
Recommendation 1A: Streamline the Assurance System

A number of informed observers—including some within OPRR itself—have come to believe that the existing assurance negotiation process has lost much of its original utility and has instead become unduly bureaucratic and cumbersome. While the process had important educational components in the early years of federal regulation, now that research institutions have become more sophisticated in this area, its time may have passed. Dr. Gary Ellis, testifying before the Subcommittee on Human Resources of the Committee on Government Reform and Oversight of the United States House of Representatives, acknowledged as much.41

The most consistently proposed change that is relatively easily implemented (i.e., without any regulatory modification) involves transforming the assurance system into a simplified registration system. Streamlining the present assurance system would allow precious resources to be redirected to higher priority activities, including education and a more rigorous IRB performance-monitoring system. (Redirection of existing resources alone is unlikely to be sufficient to meet the full need but would be a good first step.) For example, if a registration model is adopted, instead of negotiating each assurance, OPRR would require each regulated entity to register with OPRR, providing the minimal amount of information required by the regulations.42 This approach would preserve the essential tether of the government to the system of institutional protections for the purposes of education and, when necessary, compliance oversight.

Recommendation 1B: Achieve Consistency Across the Government—Require Full Adherence to the Common Rule

Across the federal government the uneven application of existing regulations requires improvement: Even after President Clinton's 1994 directive, not all federal agencies subscribe formally to the Common Rule, and among those that do the level of adherence is mixed. NBAC staff are studying current levels of compliance among federal agencies. Any recommendations formulated by NBAC should explicitly require—at a minimum—government-wide compliance with human subject protection regulations.

Recommendation 1C: Achieve Consistency Across the Government—Unify Government Oversight

In addition to requiring all government agencies to adhere to the Common Rule, NBAC should recommend unification of government oversight of human subjects in one federal agency or office. Given the uniform positive reviews from a variety of observers for OPRR's expertise and effectiveness, this function should be assigned to OPRR, although the structure will require modification both to address the independence of the monitoring function. (See Recommendation 1D below.) Separate FDA jurisdiction over drugs, medical devices, and biologics should be retained, but FDA and the OPRR successor should enter into a Memorandum of Understanding to coordinate their functions and reduce the burden on multiply regulated entities. See further detail on this topic below.

Recommendation 1D: Assure Independence of the Government's Monitoring Function

As noted by multiple observers from GAO to DHHS OIG to Drs. Fletcher and McCarthy, OPRR's placement within DHHS presents serious structural problems that must not be perpetuated. A supplemental statement issued by GAO in response to congressional questions following the presentation of the GAO report noted: "...a potential weakness exists because NIH is both the regulator of human subject protection issues as well as an institution conducting its own human subject research. The Director of NIH, therefore, has responsibility for both the success of NIH's intramural research program and for the enforcement of human subject protections by OPRR."43 An approach for resolving these structural conflicts of interest must be incorporated into any proposed federal oversight mechanisms. The most obvious mechanism is to move OPRR (or any successor office/agency) out of NIH and place it elsewhere within the executive branch. Any successor office/agency should have the weight of authority necessary to carry out its mission, as well as the necessary resources. See Section IV below.
Recommendation 1E: Provide Adequate Resources

The current OPRR does not have enough staff or a large enough budget to meet its current mandate adequately, let alone to execute expanded responsibilities. It should be of serious concern that the financial commitment of DHHS to human subject protection, measured in financial terms, has been declining over time, even while research funding is increasing. While it is likely that additional resources are required to meet existing compliance oversight responsibilities, it seems without question that current resources for educational programs are inadequate. The consistency and quality of any decentralized system is necessarily dependent upon careful and continuing education of participants across sites. Documented deficiencies in the operation of IRBs call for more educational efforts and performance assessments; these tasks cannot be undertaken for research under OPRR's current purview without additional resources. These costs should be assessed and addressed in addition to the projected costs for any new responsibilities. Mechanisms for addressing these shortcomings must be incorporated into any NBAC recommendations.

Reviews of the performance of OPRR in protecting subjects repeatedly show that it has the ability to address these shortcomings, but does not have sufficient resources for doing so. OPRR comes up short in any measure of educational activities, site visits, and timely resolution of allegations of noncompliance—to the detriment of current human research subjects.

Assuming identified deficiencies in the existing oversight system are corrected, then NBAC can move to considering expansion of federal jurisdiction in its effort to improve the federal regulatory system for the protection of human subjects. Rather than expanding regulation globally, however, and then finding mechanisms for removing low- or no-risk research from its purview, this paper recommends a different approach.

III. Issues Involved in the Expansion of Federal Oversight

Beyond the responsibility of the federal government to address known deficiencies in our system, we also know that there are human research subjects who are not receiving basic federal protections and who should be. How to provide those protections effectively—identifying the core protections to be provided around which societal consensus exists, focusing upon serious risks and with a reasonable cost/benefit ratio—is the challenge. NBAC must fully understand the gaps in current protection and practical problems that must be solved before recommending an expansion of federal oversight to encompass privately conducted research.

A. Gaps in Federal Protection

The OIG report on IRBs and the ACHRE report illustrate places where even research that is covered by federal regulation may not be receiving meaningful or accountable oversight. Beyond that, current federal regulations for protection of human subjects do not reach: research conducted or funded by federal agencies not subscribing to the Common Rule; research that is not federally funded conducted at institutions with SPAs and not covered by that institution's assurance; and privately conducted research that is not subject to FDA jurisdiction. In none of these areas can it be assured that NBAC "twin protections" of informed consent and independent review are provided.

Dr. Gary Ellis, Director of OPRR, and others have offered examples where potentially harmful research has been reported, but where the subjects are not protected by federal regulation. Recent news reports about Viagra, the "male potency pill" contain references to clinics beginning their own research on its effects on women. (See Attachment A.) Are the participants in those efforts likely to receive the twin protections of informed consent and independent review of the risks? Do we, as a society, believe they should?

And what about the students and families about whom information would be stored in the database described in a January 1997 report in the Washington Post? (See Attachment B.) That report described a school district implementing a student database that would let schools compile medical and dental histories and
records of behavioral problems, learning disabilities, and family income. The newspaper report indicated that the new database would allow "administrators to monitor whether students of a particular ethnic background or sex were doing better or worse than others in English, algebra or any other course....a broader database would help administrators examine demographic, academic and extracurricular information in an effort to pinpoint causes and solutions."** Such databases could also provide a rich resource for researchers, but research uses are not currently regulated.

Other examples abound. They include research conducted at or by:

- **Some in vitro fertilization clinics:**
  
  Example: women who had experienced multiple miscarriages alleged that they were misled about the substantial financial cost of participating in research to pregnancy.* (See Attachment C1: OPRR had no jurisdiction to review these complaints because this research was not subject to any assurance.)

- **Some weight loss or diet clinics:**
  
  Example: OPRR received a complaint about a coercive structure of payment for participation in weight loss research that made it extremely unlikely that the subjects would discontinue participation prior to the completion of research.* (See Attachment C2: OPRR had no jurisdiction to review these complaints because they occurred at unregulated entities.)

- **Some physicians' offices:**
  
  Example: a woman who had been treated for breast cancer alleged that identifiable private information from her medical record had been placed in a registry and made available to research investigators without her consent.* (See Attachment C3: OPRR had no jurisdiction to review these complaints because treatment was not provided under any research protocol, and the assurance of the hospital maintaining the registry covered only DHHS-supported research. DHHS did not provide any support for the development or maintenance of the registry.)

  *and* a December 1996 publication in a professional journal for reconstructive surgeons describing a prospective study comparing lateral and standard face lifts; there is no indication that patients were aware of or consented to their inclusion in the study.* (See Attachment C4.)

- **Some dentists' offices:**
  
  Example: a 1995 university news release describes private-foundation funding of a dentist's study of removal and replacement of mercury amalgam dental fillings from approximately 30 patients.* (See Attachment C5.)

- **Some psychotherapists' offices:**
  
  Example: OPRR has received complaints from patients subjected to "experimental" psychotherapy techniques, but had no authority to investigate the complaints, because their practitioners were not affiliated with any regulated entity.* (See Attachment C6.)

- **Some corporate and industrial health safety and fitness programs:**
  
  Example: attempts to enhance the physical fitness of loss prevention officers involved collection of data (e.g., activity monitoring) that would likely reveal unsatisfactory job performance.

  *and* "team management" research in which unsuspecting individuals were subjected to a sham robbery, resulting in significant stress, fear, and anxiety* (see Attachment C7); another complainant to OPRR described "fright response" research in which participants were subjected to unexpected and disturbing visual stimuli.
Some developers of genetic tests:
Example: the Task Force on Genetic Testing of the National Institutes of Health/Department of Energy Working Group in Ethical, Legal, and Social Implications of Human Genome Research reported in May 1997 that a substantial number of genetic tests are being developed without the oversight of IRBs. Twenty-six percent of 140 not-for-profit organizations developing genetic tests had not submitted any protocol for review; 41 percent of 54 biotechnology companies had not submitted any protocol for review.59

Colleges and universities not receiving federal research funds:
Example: research presented in 1997 at a national conference of English professors in which the researchers displayed notes taken by psychotherapist during work with a real client including name and other identifying information on that client, revealing a history of sexual abuse and suicidal tendencies. Given the content of federal regulations and the conventions observed by reputable IRBs, it seems most unlikely that this research was ever reviewed (or approved) by an independent review body.58 (See Attachment C8.)

Some federal research conducted under the auspices of agencies not subscribing to the Common Rule:
Example: The National Endowment for the Humanities does not subscribe to the Common Rule. As a result, unless the home institutions of the researchers have negotiated MPs with OPRR, the research announced in an April 1998 report in the Chronicle of Higher Education might—or might not have—received IRB review at the home institutions. The research projects announced include projects on topics such as "Children's Developing Knowledge of How to Create Words: A Study in Linguistics," "West African Infant Care Practices," and "Bilingualism in an Immigrant Community." Without further information, it is hard to tell whether issues of confidentiality were fully addressed before this research was initiated or whether any independent body reviewed the effects of participation on the children.

Research by unregulated entities:
Example: Nishimi's 1994 congressional testimony referenced research funded by a pharmaceutical company in which private physicians were given grants to identify children of short stature.57 (See Attachment C9; OPRR had no jurisdiction over the research because no regulated entities were involved.)

Other research-related activities that could, and in some cases information exists to suggest they already have, present risks to human subjects include health services research and internal evaluation research. Health services research is increasingly common as managed care becomes more pervasive and typically involves efforts to measure efficacy and cost-effectiveness of various treatments in managed care organizations. Internal evaluation research involves comparisons of management techniques, labor practices, and other corporate research into how employees like or perceive their work environment. It will be a challenge to find the lines between benign surveys of employee satisfaction and more intrusive and/or coercive research that could compromise employee privacy. But while some of these examples are more egregious violations than others, none of them are currently regulated unless the research is funded by one of the Common Rule agencies.

B. Practical Problems in Expanding Federal Oversight
What might be the consequences of expanding the current definition of research and applying it globally to all research involving human subjects? More particularly, what is the wisdom, practicality, and cost-effectiveness of bringing a potentially broad range of activities under the scope of federal regulation?

1. What Should Be the Definition of "Research"?
Global applicability of the current definition of research could encompass many activities that impose very little or even no risk to subjects of that research. While the scope of federal protection is narrow, the current definition of research used for regulated activities is very broad:
'Research' means a systematic investigation designed to develop or contribute to
generalizable knowledge.\textsuperscript{39}

Many forms of polling, much market research, and arguably some forms of journalism could be considered
"systematic investigation designed to develop or to contribute to generalizable knowledge" that is obtained
"through intervention or interaction" with individuals or that involves "identifiable private information" about
those individuals. Differentiating between activities that should be covered and those for which expanded
federal regulation might be burdensome could consume significant resources and time on the part of many
individuals and could prove divisive and distracting from the goal of protecting Americans from risk of serious
harm through participation in research.

Should the current definition be used as is, or could it be modified to avoid such a result? The current
definition was purposefully designed to be assure that subjects of research would be protected—whatever the
research might be. Appendix Two of the Belmont Report (the report of the National Commission) contains a
number of commissioned papers, at least four of which address the boundaries between research and therapy.\textsuperscript{39}
These papers were commissioned as part of the National Commission's formulation of its recommendations,
including the definition of research in its final report.

When that definition was published in the Federal Register, only 21 comments addressed the proposed definition
of research in the rulemaking process.\textsuperscript{60} The commentary accompanying the final regulation in January
1981 characterized those comments as follows: "While a few commentators favored the proposed definition
because it offered flexibility to the IRB, a majority of the twenty-one opposed or raised questions about the
definition. Several commentators felt that the definition is too broad and should be restricted to biomedical
research...."

The DHHS Response to the comments observed that:

HHS believes that public concerns that the definitions are too broad will in most cases be met
by the exemptions from the regulation. The National Commission, although not identifying
specific fields of research, clearly intended to include behavioral studies in the recommended
definition of 'research.' HHS agrees with this conclusion and does not believe that the defini-
tion of 'research' violates the rights of investigators given that the regulations exempt research
which offers little or no risk to the rights and welfare of human research subjects.\textsuperscript{81}

While one approach to the problem of sweeping low-risk research into an expanded federal regulatory
scheme is to narrow the definition of research, the continuing progress of scientific advances applicable to
human treatment suggests this is not a sound approach. No better definition of research than that currently
used has attracted consensus support in the almost 30 years this definition has been in place. In the absence
of a tested alternative, altering the definition itself seems unwise.

If the present definition is perpetuated rather than modified, it is likely that development of new exemptions
should be considered to obviate unintended consequences of expanded regulatory scope and to focus government
protections upon areas posing the greatest medical and ethical risks. It should be possible to craft appropriate
exemptions for very low-risk "research." In approaching such a task, the risk of harm must be balanced with
the burden of regulation. On the other hand, given the extended and somewhat tortuous process required to
develop and refine the current definitions and exemptions, some caution seems warranted. Before NBAC makes
recommendations that might require the development of new exemption categories, alternatives should be
carefully considered.

For example, not only would it be necessary to develop consensus across a broad spectrum of constituencies
about new exemptions, but regulatory language would need to be carefully crafted and tested. Based on ex-
perience, this might well take a period of years. Would the entire process of expanding the twin protections of
informed consent and IRB review be delayed in the meantime, or would we go through a period in which potentially harmless or very low-risk activities would undergo unnecessary review? If the latter, what long-term effects might that have for a system that by many accounts is already overburdened and near the breaking point?

2. Who Decides an Activity Is Exempt? Conflict of Interest Questions

After the development of appropriate exemptions and embodying regulatory language, still another practical problem arises: Who will determine the applicability of the exemptions? It is fundamental that a person performing research has a conflict of interest in deciding that his or her research is exempt from review. This implies independent review, which raises a raft of troubling questions: Who will perform these reviews? How much paperwork will it require? For researchers not affiliated with universities, where will they find an appropriate IRB? Will this intensify existing incentives for a proliferation of for-profit IRBs? Might core ethical examinations be diluted by expanding the workload of IRBs along with the requirements for paperwork and review of low-risk research? At what cost might this occur?

The prospect that expansion might divert valuable resources and energy from projects needing thoughtful ethical review is troubling. It is not difficult to envision the creation of an extensive and burdensome, possibly profit-driven, rubber-stamping review system that dilutes attention to the serious ethical issues that research involving human subjects can imply. This is an outcome no one seeks. Further, the costs are potentially very large.

3. Costs

The costs involved in globally extending the current system could be significant. One indicator of the possible costs is that each (single-site) protocol review by Independent Review Consulting, Inc., (a reputable for-profit IRB that provides IRB services for unaffiliated investigators) costs $1,200. This does not, of course, include the costs involved in preparing materials to be reviewed by the IRB. Assuming that the direct costs of non-institutional review boards are comparable to those of academic IRBs, very large sums of money (representing the costs of creation, review, and maintenance of required information) could be at stake in a dramatically expanded system of human subject protections, especially those involving low-risk activities. The cost/benefit ratio for such an approach does not seem advantageous, especially in today’s political environment.

Recommendation 2: Expand Regulation Incrementally, Not Globally (at Least at First)

This recommendation proposes an alternative to expanding the scope of federal regulation very broadly and then crafting appropriate exemptions. It suggests adding targeted areas to the scope of federal oversight areas of research. Two possible mechanisms are proposed for NBAC’s consideration.

Recommendation 2A: Expand Jurisdiction Incrementally as “Known Risks” are Identified

As a starting place, NBAC might focus upon the goals articulated by the President of protecting subjects from unwitting participation and undue risk by focusing upon targeted areas. Given the estimate of the ACHRE that “40 to 50 percent of human subjects research poses no more than minimal risk of harm to subjects,” it is all the more critical to focus any new regulatory energy on activities that put human subjects at risk. While we cannot know if ACHRE’s estimate will extrapolate to presently unregulated activities, it is a reasonable starting point for thinking about these issues.

The goal should be to define areas of national concern by focusing on documented instances where human subjects have been exposed to:

- unwarranted risks,
- where they have been induced to participate in research without full understanding of those risks (or of the remoteness of personal benefit to them from the participation); and
where the protocols have not been subject to independent review for compliance with generally accepted standards of research involving human subjects.

The targeted areas would focus on categories of “known risks”—research that we know puts human beings at risk, whether conducted privately or with federal support. An incremental approach seems more consistent with current trends in public policy, while still providing appropriate protections to residents of this country who participate in risky research activities. This approach would be more amenable to a documented cost/benefit analysis, and thus might be more persuasive to the public and to lawmakers. Adopting this recommendation implies the development of categories requiring protection and procedures for invoking that protection. At first glance, likely candidate categories include:

- all unapproved, invasive procedures (e.g., work performed at in vitro fertilization clinics) that involve genetic tests;
- research conducted at institutions with a research mission (primarily universities) receiving federal funds, but that is not directly federally supported (see below); and
- other research posing documented risks to participants as gleaned from reports of problems.

Another, more controversial, category requiring serious examination is research that involves dignitary damage or breaches of confidentiality leaving the subject at risk.

An effort to identify and document known risks implies significant work, but this effort will likely be more productively expended—and generate greater support—than that required to extend the present regulatory system to cover “all” research.

**Recommendation 2B: Explore Expanding OPRR’s Jurisdiction Without Statutory Change**

Historically, OPRR has taken the position that the language of the Public Health Service Act requires mandatory compliance with its provisions only for research that is actually funded in whole or in part by DHHS. Thus, institutions filing an MPA voluntarily agree to apply federal regulations for human subject protections to non-DHHS research. Institutions that file SPAs have no obligation to ensure IRB review or informed consent for any other research involving human subjects. This may well be a more conservative interpretation of the Act than it requires.

**NBAC should seek assistance and advice from the DHHS Office of the General Counsel to determine whether a broader reading of this statute is permissible.** Specifically, “research” is not qualified in Sections 491(a) and (b)1 and refers to any biomedical or behavioral research involving human subjects. **Can the Act be read to refer to all research at any institution supported by DHHS funds, not just research that is directly supported by DHHS?**

Further advice and legal review will be necessary to explore this possibility. Such an expansion of OPRR’s jurisdiction will require a considerable addition of resources to OPRR. While seeking such advice may seem burdensome, the possible gains for regulated entities and for governmental efficiency warrant the effort.

**IV. Possible Structures for Unified Federal Oversight**

Whether NBAC decides to expand federal jurisdiction to encompass areas of known risks or to pursue more global federal jurisdiction, a different federal structure will be needed than is now in place. Deficiencies of the existing system that should be addressed in any proposed reforms should include more consistency and coordination across the government, as well as in the government’s interactions with regulated entities. Given the size of the federal government and the vast array of research sites across the country, NBAC should seek a structure that will provide a single office that works in a distributed style. Some existing agencies or offices that
currently function in this way provide models that have much to offer as exemplars. These include the Office of Governmental Ethics (OGE), the Office of Special Counsel (OSC), and the Nuclear Regulatory Commission (NRC). Although different in size and mission, each has educational and compliance-monitoring responsibilities, and each operates in a decentralized, distributed fashion.

Before considering the placement of the human subject protection monitoring system, one most important issue must be addressed—namely, in a unified federal oversight system, what should happen to the current functions represented in OPRR and FDA?

A. Unify OPRR and FDA?

Although it is always simpler from the perspective of a regulated entity to have only one federal oversight office, the missions of OPRR and FDA are sufficiently distinct that a strong case can be made that their independent functions should be maintained. Further, this is clearly the most pragmatic solution, since they currently operate under two distinct statutory authorizations, and the political ramifications of attempting a unification seem more complex and difficult than the gain would warrant. FDA and OPRR currently work in a coordinated fashion and have significant overlap in their approaches to regulated entities.

Thus, NBAC should recommend that these separate functions—drug and medical device approval and research oversight—should remain the primary province of FDA and the OPRR successor, respectively. The OPRR successor should be responsible for all regulated research involving human subjects, both government wide, and whatever private research is added to the regulatory structure.

To enhance coordination and cooperation, the two agencies should enter into a Memorandum of Understanding that addresses interagency cooperation and jurisdiction and establishes a formal coordinating function. This should include new agreements covering IRB oversight to assure that the protection of human subjects is addressed in a reasonable, cost-effective way, especially in light of the GAO’s cautions about the substance of FDA IRB reviews and of concerns voiced by regulated entities about the sometimes burdensome nature of joint (and uncoordinated) jurisdiction by two federal agencies over the same IRBs.

NBAC or the successor agency may need to commission an examination of other special-purpose agency IRB regulations (for example, those at the Centers for Disease Control and perhaps the Department of Energy and/or those in classified settings) to determine whether other accommodations or Memoranda of Understanding might facilitate appropriate regulatory oversight.

B. Possible Models

The following existing governmental offices offer insights into possible models for an OPRR successor office that would oversee all human subject research.

1. OGE

The mandate of the OGE is to prevent ethical misconduct within the executive branch; it has responsibility for the prevention of conflicts of interest and for resolving those conflicts of interest that do arise. There are five applicable federal statutes for which it has enforcement responsibility. The Office of Public Integrity in the Department of Justice reviews OGE ethics opinions because it has enforcement authority for the underlying criminal statutes.

Created in the aftermath of the Watergate scandal, OGE was originally located within the Office of Personnel Management. During the Reagan administration, OGE became an independent agency. The Director is appointed by the President, with the advice and consent of the Senate, but that is the only politically appointed position in the agency. The remainder of the staff, about 80 people, are civil service employees. In contrast, OPRR has around 17 full-time staff members devoted to human subject protection (out of 28 total staff members). OPRR’s
FY 1995 budget was $2.25 million. Its FY 1996 budget was $2.13 million, and its FY 1997 budget was $2.10 million, a little more than half of which was spent on human subject protection activities.

OGE promulgates standards of conduct based on 14 fundamental principles. Its advisory opinions and ethical guidance are widely disseminated in the federal ethics community to assist in keeping officials informed and up to date. OGE oversees a broadly decentralized program in which each federal agency names a Designated Agency Ethics Official (DAEO); these 144 officials report jointly to the head of the agency and to OGE. This model seems particularly relevant when considering a government-wide human subject protection function.

OGE supports the DAEOs by developing educational materials and conducting training workshops for them and the other staff in each agency with responsibility for ethics compliance, who together comprise what is known as the federal “ethics community.” There are close to 12,000 part-time members of the federal ethics community, with about 400 of them serving on a full-time basis. While OGE audits their performance on a regular basis, the DAEOs hold significant responsibility within their agencies for educational programs and for compliance with congressional and presidential directives. This model of distributed responsibility dovetails nicely with the local control philosophy of federal oversight for research involving human subjects.

Although OGE focuses its efforts on education and providing positive guidance in response to questions, it also maintains a significant audit program, with 27 full-time auditors. These auditors review advice provided by DAEOs, the content of agency ethics training programs, and required financial disclosure forms. When violations of the standards of conduct are substantiated, they can lead to administrative sanctions (including reprimands, time off without pay, and/or demotion). Violations of the five applicable statutes carry higher penalties. OGE has 77 full-time employees and an annual budget of $7.6 million. See Attachment D for further information on OGE.

OGE’s independence from other government agencies presents an example that would cure the structural deficiencies found in OPRR’s placement within an agency that it must also monitor for compliance, as cited by GAO and Drs. Fletcher and McCarthy. At the same time, the joint reporting status of the DAEOs presents an interesting model that balances working within each agency’s individual culture while achieving consistent policy interpretation. Further, its independent standing emphasizes the importance of the issue it monitors and insulates it from political pressures. Finally, the distributed model could prove equally strong in the setting of regulated institutions.

On the other hand, OGE’s independent status and relatively small size may also reduce its leverage in budgetary processes, as it may not always have a seat at the table when budgetary compromises are reached. Embedded within a larger federal agency, budgetary negotiations have a different complexion. It is difficult to predict the quality and consistency of top-level attention to issues of human subject protection if those responsibilities are placed in an independent agency or department, especially in periods lacking in public focus on these issues.

2. OSC

The OSC was originally part of the U.S. Merit Systems Protection Board, but became “an independent federal investigative and prosecutorial agency” in July 1989. The principal responsibilities of the OSC are three-fold: 1) investigating allegations of prohibited personnel practice; 2) interpreting and enforcing the Hatch Act (political activities of federal employees); and 3) operating a whistleblower disclosure hotline to receive information “about wrongdoing in government.” The OSC’s role was expanded in 1994 to include investigation and prosecution of cases involving the denial of federal employment rights to veterans.

The President appoints the head of the agency, the Special Counsel. The remainder of the staff, about 95 civil service employees, report to the Special Counsel to carry out OSC’s responsibilities. OSC’s 1998 budget was $8.4 million.
Although OSC's responsibilities are primarily executed within the executive branch, it serves as a useful model for NBAC because of its ability to work in a distributed, decentralized way across the full range of federal agencies. For example, OSC has jurisdiction to investigate allegations of prohibited personnel practices within any executive branch agency. These investigations are frequently conducted in conjunction with other government agencies. This model is particularly useful when thinking about oversight of intragovernment activities. See Attachment E for further information on OSC.

3. NRC

Holding wide regulatory and compliance responsibilities, the NRC operates on a completely different—and much larger—scale than the previously discussed offices. Established as an independent agency in 1974 by the Energy Reorganization Act, the purpose of the NRC is to "ensure adequate protection of the public health and safety, the common defense and security, and the environment in the use of nuclear materials in the United States." The NRC's responsibilities include regulation of commercial nuclear power reactors; medical, academic, and industrial uses of nuclear materials; and the transport, storage, and disposal of nuclear materials and waste. The NRC adheres to five Principles of Good Regulation that encourage ethical performance, openness to the public, efficient management and administration, clear regulations, and reliability.

Five commissioners are appointed by the President and confirmed by the Senate for five-year terms. One of the appointed commissioners is designated by the President to function as the chairman. A civil service staff reports to an executive director, who executes the directives of the commission. The overall structure and organization of the NRC provide NBAC with another established model of an independent agency that works in a distributed way within federal agencies and at diverse academic and private sites throughout the country. Further, it provides a model to examine when considering suggestions, such as Dr. Fletcher's, that OPRR (or its successor) needs a citizen advisory panel.

Divided into divisions with specific responsibilities, the NRC has educational and compliance responsibilities similar to those of the OPRR, albeit on a much larger scale. Among its multiple divisions are one with responsibility for regulatory programs and another with responsibility for oversight and investigations. An Office of State Programs coordinates NRC activities with state and local governments as well as with other federal agencies and the sovereign Indian nations. NRC has 3,000 employees and an annual budget of $468 million. See Attachment F for further information on NRC.

Given the magnitude of NRC, it is somewhat difficult to make relevant comparisons to how this model might operate if translated into the human subject protection area. One possibility is that NBAC, or some similarly constituted commission, could serve as the policymaking body, with OPRR and FDA staffs carrying out their present roles. In such a configuration, perhaps the OPRR (research-oversight) function would fall under the NBAC successor function while the FDA staff would remain in that agency but have dual policy guidance.

If NBAC or a successor commission were to serve as the policymaking or advisory body for an OPRR successor, two issues must be addressed: 1) NBAC's present expiration date (authority for human subject protection cannot be allowed to expire) and 2) the need for a revised charter to provide formal regulatory authority.

Recommendation 3: Explore Existing Models of Federal Offices/Agencies with Both Educational and Compliance Responsibilities—Design NBAC's Recommendations Based Upon Those Models

Devising an improved governmental structure for a unified human subjects protection system will take expertise beyond the scope of this paper. Aside from explorations of the policy and political implications of its recommendations, NBAC will need to commission legal analyses of what enabling legislation or regulation will be necessary to effect any structure it suggests. NBAC must also address—perhaps through additional commissioned papers or through advice from established governmental mechanisms—reasonable resource allocations for the expanded functions it envisions.
Because this problem has been so intractable for so long, I encourage NBAC to provide specific instruction and draft legislation as part of its final report to the executive and legislative branches. Otherwise, its recommendations could well become just one more report sitting on a shelf.

V. Conclusion

In its June 1998 report, the OIG of DHHS found significant cause for concern in the current operation of our human subject protection system. While the OIG found no “widespread abuses of human research subjects,” its report identified aspects of our current system in pressing need of reform. This report does not stand alone: The observations of the OIG echo and reinforce those of multiple other observers of the current system, including many inside the government who hold responsibilities for protecting human subjects of research.

The challenge for NBAC is to devise recommendations for assuring substantive ethical consideration of the serious issues present in human subject research that can be enacted in the current political environment. This means addressing identified deficiencies in our current regulatory scheme, filling in some of the known gaps representing areas of real risk to residents of this country who participate in research, and assuring true accountability for this regulatory system in a cost-effective manner.

Responding to these challenges requires retooling the existing federal structure to provide cleaner lines of authority, uniform implementation of existing rules across the government, and streamlined links between the government and local IRBs.

Research subjects—particularly those who are not told they are participating in experimental activities or those participating in research that has not received prior independent ethical review—are among the most vulnerable of our population. In permitting their rights, welfare, and dignity to be compromised, we compromise our own.

It is time to finish the job of protecting human subjects that began more than three decades ago.

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Attachments


C1: OPRR Compliance Oversight Log. Letter to Dr. Melody Lin, Compliance Oversight, NIH, received June 18, 1993. Obtained from the OPRR under the Freedom of Information Act.

C2: OPRR Compliance Oversight Log. Regarding the Newark Beth Israel Medical Center, received September 28, 1994. Obtained from the OPRR under the Freedom of Information Act.

C3: OPRR Compliance Oversight Log. Regarding the St. Vincent Hospital Medical Center, Portland, Oregon, received April 13, 1995. Obtained from the OPRR under the Freedom of Information Act.


Notes


3 To be fair, research involving human subjects encompasses a much broader range of activities than does research involving animals. Few of the difficult issues raised by behavioral research, violations of confidentiality, or invasion of privacy arise when working with animals, for example, which makes the prospect of more broadly regulating research on humans more complex in some ways than devising regulations for the appropriate treatment of animal subjects of research.


6 Estimates of the number of IRBs operating in the United States range from around 3000 to more than 5000. OPRR oversees 700 IRBs associated with MPAs; about 1250 associated with Cooperative Project Assurances; and around another 3000 associated with SPAs. Personal communication from Tom Puglisi, OPRR, to C. K. Gunsalus, September 1998.


12 Nishimi testimony, pp. 149–150.


"Unless otherwise required by department or agency heads, research activities, in which the only involvement of human subjects will be in one or more of the following categories, are exempt from this policy:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability, or be damaging to the subjects' financial standing, employability, or reputation.

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

4. Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available, or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

5. Research and demonstration projects, which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

6. Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed, or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration, or approved by the Environmental Protection Agency, or the Food Safety and Inspection Service of the U.S. Department of Agriculture."
14 45 CFR 46.110. Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.


16 Nishimi testimony, pp. 162–163.

17 21 CFR 56 155 (b) states: "The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner." OPRR's authority to investigate derives from the Public Health Service Act, as amended by the Health Research Extension Act of 1985, Public Law 99–158, November 20, 1985, Section 491(2) which states: "The Secretary shall establish a process for the prompt and appropriate response to information provided to the director of NIH respecting incidences of violations of the rights of human subjects of research for which funds have been made available under this Act. The process shall include procedures for the receiving of reports of such information from recipients of funds under this Act and taking appropriate action with respect to such violations."

18 Nishimi testimony, p. 162.


20 45 CFR Part 46.103(a).


22 There is one MPA institution in Canada (McGill). Statistics on OPRR assurances and oversight in personal communication from OPRR to C.K. Gunsalus, August 10, 1998.

23 Statistics on OPRR caseload from personal communication, Gary R. Ellis to C.K. Gunsalus, April 1998.


27 Testimony of Dr. Gary B. Ellis, Director, OPRR, Office of Extramural Research, NIH, DHHS, before the Subcommittee on Human Resources, of the Committee on Government Reform and Oversight of the U.S. House of Representatives, June 11, 1998.


30 Ellis testimony.


32 President Clinton's Order directs that all departments and agencies of the government "cease immediately sponsoring or conducting any experiments involving humans that do not fully comply with the Federal Policy." Memorandum for the Vice President, the Heads of Executive Departments and Agencies, Subject: Review of Federal Policy for the Protection of Human Subjects, February 17, 1994.


34 Nishimi testimony, p. 157, footnote 3.


36 Testimony of Sarah F. Jagger, Director, Health Financing and Public Health Issues, Health Education and Human Services Division, U.S. GAO, before the Committee on Governmental Affairs, U.S. Senate, March 12, 1996.
38 Scientific Research: Continued Vigilance Critical to Protecting Human Subjects, p. 20.


40 Ibid.

41 Ellis testimony.

42 45 CFR Part 46.103(b) requires that each institution provide certain specific information to OP RR.


45 Letter from Dr. Gary B. Ellis, Director, OP RR to James F. Childress, Ph.D., Chairman, Human Subjects Subcommittee, NBAC, April 10, 1997.


58 45 CFR 46.102: “Human subject” means a living individual about whom an investigator, (whether professional or student) conducting research obtains (a) data through intervention or interaction with the individual, or (b) identifiable private information.

“Intervention” includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes.

“Interaction” includes communication or interpersonal contact between investigator and subject.

“Private information” includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information), in order for obtaining the information to constitute research involving human subjects.”


61 Ibid. At the same time, other changes were made in the Belmont Report's proposed definition. In response to other concerns about the breadth of the proposed definition of research, DHHS inserted the term "living" into the definition of human subject to clarify that historical and biographical research were not covered. The final regulation also used "private" to modify "information" to make it clear that the "regulations are applicable only to research which involves intervention or interaction with an individual or identifiable private information." Private information was clearly defined, with the following concluding comment: "It is expected that this definition exempts from the regulations nearly all library-based political, literary and historical research, as well as purely observational research in most public contexts, such as behavior on the street and in crowds."

