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FEDERAL RESEARCH COMPLIANCE: BIOMEDICAL & RESEARCH INTEGRITY ISSUES

By Robert J. Kenney, Jr., Barbara F. Mishkin, Michael F. Mason, and Michael J. Vernick

The Federal Government's support of biomedical and other scientific research through grants, cooperative agreements, and contracts is the lifeblood of the U.S. research community, but that support comes with a price. Inextricably tied to federal support are a multitude of increasingly complex legal obligations and potential liabilities derived from statutes, regulations, and policy statements that are included in the terms and conditions of the awards of federal research funds. These rules and regulations, enforceable through administrative, civil, and even criminal penalties, touch virtually every aspect of the research process and place substantial burdens and responsibilities on the recipients of federal research support. Research institutions increasingly recognize that survival in this regulatory regime requires significant resources and an affirmative and carefully planned compliance program. The critical first step toward an effective research compliance program—although by no means the only step—is to understand what the applicable rules are and to keep up with their frequent changes.

This BRIEFING PAPER is the second of two recent PAPERS addressing compliance issues associated with federally supported research. These issues are broad ranging and affect thousands of colleges and universities, medical centers, and other research institutions conducting billions of dollars of federally funded research annually. The earlier PAPER focused on finan-

IN BRIEF

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cial and administrative research compliance issues.[1] This PAPER examines a variety of other compliance issues affecting federally supported biomedical research, including the rights and welfare of research subjects, research integrity, and safety. Specifically, the PAPER discusses the requirements and the compliance implications of federal rules governing (1) the protection of *human research subjects*, (2) the use of *human pluripotent stem cells*, (3) the care and use of *laboratory animals*, (4) *biosafety*, (5) *financial conflicts of interest*, (6) *research misconduct*, and (7) *data privacy*. In addition, the PAPER (a) provides a brief overview of a recent initiative by the *National Institutes of Health* to enhance regulatory compliance through the use of "*proactive compliance site visits*" and (b) concludes with some advice for research institutions on transforming the substantive information on the complex rules discussed in this PAPER into *effective compliance programs*.

Human Research Subjects

■ HHS Regulations

Alleged inadequacies in the protection of research subjects—occasionally associated with highly publicized deaths—attract the attention of the research community, the Congress, the press, and the enforcement arms of the Department of Health and Human Services. The latter include the HHS Office of Inspector General and the Office for Human Research Protections (OHRP) (successor to the Office for Protection from Research Risks).[2] Much of the attention has focused on the extent to which institutions are complying with the HHS regulations for the protection of human subjects[3] and the effectiveness of institutional review boards (IRBs) in overseeing that research as required by the Public Health Service Act.[4]

Subpart A of the HHS regulations, which has been adopted by 17 other departments and agencies and is known as the "Common Rule," sets forth the policies and procedures that govern informed consent and IRB review of federally supported research involving human subjects.[5] Research that is not federally funded but that involves investigational new drugs and devices (which are regulated by the Food and Drug Administration) must also be reviewed and approved by an IRB in accordance with the Common Rule.[6] Moreover, virtually all institutions receiving NIH research funds promise to submit all research involving human subjects to IRB review, whether or not federally funded. In addition to the provisions of the Common Rule, the HHS regulations include special protections pertaining to research involving the human fetus, pregnant women, and in vitro fertilization; research involving prisoners; and research involving children.[7]

Although the scope of the Common Rule is broad, there are several exemptions for research that presents no more than minimal risk to the participants. These include, for example, certain research conducted in an established educational setting and involving "normal education practices."[8] Likewise, research involving the collection or study of existing records or biological specimens is exempt "if these sources are publicly available or if the

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information is recorded by the investigator in such a manner that subjects cannot be identified, either directly or through identifiers linked to the subjects."[9]

■ HHS vs. FDA Regulations

In addition to the HHS regulations that apply to research supported by the NIH and other components of the Public Health Service, FDA regulations provide similar protections for human subjects in research involving products regulated by the FDA.[10] Specifically, the FDA regulations apply to clinical investigations that support applications for research or marketing permits for products regulated by the FDA under the Food, Drug, and Cosmetics Act. These include food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products.[11] Although the FDA's regulations address both informed consent and IRBs and are similar to those of the HHS, there are differences relating to the different subject matter regulated by the FDA. For example, the FDA has rules for emergency use of a test article (which is exempt from prospective IRB review)[12] but not for waiving or altering informed consent because the FDA, in contrast to the HHS, does not regulate the types of research that would qualify for such waivers. IRBs at institutions conducting research involving human subjects should be familiar with both sets of regulations, aware of their differences, and understand the applicability of each.

There are many instances in which research falls within the ambit of both the FDA and the HHS regulations (for example, when the NIH supports clinical trials of a new drug or medical device). In such cases, the IRB and investigators must comply with both sets of regulations. The FDA has provided a useful side-by-side comparison listing differences between its regulations and those of the HHS.[13] The most troublesome difference for investigators and IRB members does not appear on the FDA's list. It has to do with the rules for reporting adverse events, which are discussed below.

■ Reporting Adverse Events

A critical element of the regulatory system for protecting human subjects, covered by both the HHS-promulgated Common Rule and the FDA regulations, is the reporting of serious adverse events. The Common Rule requires IRBs to have written procedures for ensuring "*prompt reporting*" to the IRB, appropriate institutional officials and the relevant department or agency head of (1) "any *unanticipated problems involving risks to subjects or others* or any *serious or continuing noncompliance* with [the regulations] or the requirements or determinations of the IRB" and (2) "any suspension or termination of IRB approval."[14] The regulations do not, however, define what is meant by "prompt" or explain what constitutes "serious or continuing noncompliance." Although guidance documents make clear that "unanticipated problems involving risks to subjects or others" means "adverse events," that critical term is not defined in the HHS regulations. The official IRB Guidebook, however, defines an "adverse effect" as "an undesirable and unintended, although not necessarily unexpected, result of therapy or other intervention (e.g., headache following spinal tap or intestinal bleeding associated with aspirin therapy)."[15]

In contrast, FDA regulations regarding investigational new drug applications provide clear definitions of "adverse experience":[16]

> Serious adverse drug experience: Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition....
>
> Unexpected adverse drug experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is

> not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

The sponsor must report an adverse experience in writing to the FDA and all participating investigators within 15 calendar days if it is both serious and unexpected, and by telephone or facsimile within 7 calendar days if it is life-threatening or fatal.[17]

All other adverse experiences and outcomes must be summarized in the annual report to the FDA and the IRB. This is another area that is not addressed in the HHS regulations but that is spelled out in detail in the FDA rules. For each clinical trial or study, the FDA must receive annual reports from the sponsor that include (a) a narrative or tabular summary of the most frequent and most serious adverse experiences, (b) a summary of all the safety reports submitted during the year, (c) a list of subjects who died, and the cause of death for each, (d) a list of subjects who dropped out in association with any adverse experiences, (e) a brief description of what has been learned during the year about the drug's actions, (f) relevant preclinical studies, and (g) significant manufacturing or microbiological changes.[18]

■ Data & Safety Monitoring Boards

An important tool for protecting human research subjects is ongoing monitoring of accumulating data. In clinical trials, serious adverse events must be reported promptly to the IRB, and the IRB may perform annual reviews of the progress of the research,[19] but that review does not provide an analysis of research data as they accumulate over the course of a clinical trial. Often, the trial is "double blind" (i.e., neither the participants nor the researchers know which of two or more treatments the individual subjects are receiving). In such studies, it is important that the investigators continue to be unaware of subject assignments until the end of the trial so that their evaluation of the subjects' responses to the treatment will not be affected by knowledge of which intervention each is receiving. At the same time, it is important for someone to keep track of results as they accumulate and know if one arm of a trial seems to be doing much better—or worse—than the other. If the trends appear to be significant, it becomes important to determine which treatment is significantly better (or worse) than the others. Sometimes, a clinical trial should be halted, either to protect subjects from an intervention that seems to have significantly more serious side effects than the others, or to provide all subjects with the treatment that has significantly better outcomes. These duties are assigned to data and safety monitoring boards (DSMBs).

DSMBs should include individuals who are not otherwise associated with the research and who possess the necessary expertise to analyze and interpret the accumulating data (e.g., biostatisticians, and clinicians). They also may include bioethicists, but their focus is always on analyzing data and deciding whether the data suggest that one arm of the study should be abandoned or the entire trial should be stopped.[20] This is especially important for clinical trials involving multiple sites, potentially risky interventions, or especially vulnerable populations.

Until recently, DSMBs monitored primarily Phase III clinical trials involving large numbers of subjects, usually at multiple sites, and typically "double blind." The NIH, however, has added a requirement for at least a *general* description of the data and safety monitoring plan for the more preliminary and much smaller Phase I and II clinical trials as part of the research application.[21] The principal investigators must submit a more detailed monitor-

ing plan to the cognizant IRB and the funding entity as part of the research protocol.[22]

■ HHS Oversight

The HHS OHRP has several responsibilities, including "developing and monitoring, as well as exercising compliance oversight" of regulations for the protection of human subjects.[23] The principal areas that the OHRP monitors include (1) the adequacy of IRB initial review of research protocols and changes to those protocols, (2) timely and thorough continuing review of each protocol, (3) prompt reporting of adverse events, (4) adequacy of the IRB minutes, (5) the IRB members' understanding of the regulations, and (6) IRB resources, records, and relevant written policies and procedures.[24] The OHRP also is concerned with the informed consent process, including whether consent documents are readable and include all required elements, and whether consent procedures are appropriate and minimize the possibility of coercion or undue influence.[25]

In recent years, the number of compliance reviews has increased substantially. The OHRP (like its predecessor, the OPRR) has demonstrated a willingness to suspend operations of IRBs and all research involving human subjects at institutions due to serious or continuing noncompliance with the regulations. Not surprisingly, the suspension of all federally supported research at a major institution can affect thousands of studies. To avoid such disruption, the OHRP instead may impose less onerous controls, such as requiring corrective action plans, education of investigators and IRB members, quarterly reporting, or prior OHRP review of certain research projects.[26]

The OHRP has made it clear that although it intends to continue its aggressive oversight program, it is interested also in working with all components of the research community to improve compliance through cooperative and interactive means. For example, the OHRP Division of Assurances and Quality Improvement (DAQI) has developed a self-assessment tool for evaluating institutional compliance with the regulations.[27] If an institution chooses, the DAQI will provide the materials and, if requested, provide feedback in writing, by teleconference or video conference, or through a site visit. Education and consultation will be offered to help the institution remedy any deficiencies, and the DAQI states that mechanisms are in place to protect the confidentiality of information voluntarily provided by the institution by a firewall between the DAQI and the Division of Compliance Oversight.[28] Although the program is still being pilot tested, institutions and independent IRBs interested in participating should contact the DAQI Director.[29]

■ New Assurance Procedures

A key component of federal oversight is the "assurance" through which institutions promise to comply with regulatory requirements for the protection of human subjects. [30] Assurances for institutions that receive HHS research funds are reviewed and approved by the OHRP. Under the Common Rule, the OHRP also reviews and approves assurances for institutions funded by other federal agencies; and the other agencies, in turn, have agreed to accept assurances filed with the OHRP for research supported by HHS or their own agency.[31] Institutions may conduct federally sponsored human subjects research only if the institution maintains an approved assurance with the OHRP.[32] On December 4, 2000, the OHRP announced a simplified process for filing assurances using a new "Federalwide Assurance" (FWA). An FWA approved by the OHRP will cover all of the institution's federally supported human subjects research. Pre-existing assurances, including Multiple Project Assurances, Cooperative Project Assurances, and Single Project Assurances, will continue to be given effect through their current expiration date or December 31, 2003, whichever occurs first. Thereafter, institutions will be required to file and maintain only an FWA. In addition, each IRB identified in an FWA must register with the OHRP. [33]

Under the FWA system, each "legally separate" entity that engages in federally sponsored human subjects research must maintain its own FWA. The new process replaces previously utilized "Inter-Institutional Agreements" and af-

filiation agreements through which one institution can rely on the IRB of another. Institutions still may designate and use an IRB operated by another organization, if the other organization agrees to the arrangement and the head of the other organization signs the FWA form signifying that its IRB is willing to review the institution's research on a regular basis.[34] OHRP guidance explains that if one institution relies on another institution's IRB on a regular basis, the parties should agree to written policies and procedures that specify their respective responsibilities for protecting human subjects.[35] If the institution wishes to rely on another institution's IRB only as part of a one-time arrangement, the institution may use the OHRP's sample "IRB Authorization Agreement for an Individual Protocol." Reliance on another institution's IRB, however, does not relieve an institution of its responsibility for maintaining an effective compliance system.

■ Education Requirements

The new FWA process also includes an education requirement. The Institutional Signatory Official (the official who has the legal authority to represent the institution named in the FWA), the Human Protections Administrator (the person with day-to-day responsibility for the institution's human subjects protection program), and the IRB Chairperson should complete the OHRP's basic educational modules or equivalent training for research involving human subjects before submitting the FWA.[36]

On October 1, 2000, the NIH implemented a similar education policy for all "key personnel" named in NIH grant applications or proposals for contracts for research involving human subjects.[37] The requirement applies to both new applications and noncompeting renewals. For grants, institutions must submit with the application a description of the education on the protection of human subjects completed by all individuals to be involved in the design and conduct of the research.[38] For contracts, the Contract Officer will request the education information at the time of the award.[39] This information may be provided in the form of a cover letter signed by the signatory official on the assurance or by another official authorized to represent the institution. Notably, the education requirement extends even to personnel who conduct human subject research that is exempt from IRB review.[40] Although the requirement also includes the key personnel of subcontractors and consultants,[41] it does not reach individuals (such as laboratory technicians) who are not involved with the human subjects portion of the project.[42]

■ IRB Accreditation

The OHRP Director, Greg Koski, has endorsed voluntary accreditation of IRBs as a helpful means of assuring quality and regulatory compliance.[43] The concept has been endorsed as well by the General Accounting Office, the HHS OIG, the Institute of Medicine, and the National Bioethics Advisory Commission.[44] Public Responsibility in Medicine and Research (PRIM&R), a Boston-based nonprofit entity known for its IRB conferences, has developed an accreditation program to be implemented by the newly created Association for Accreditation of Human Research Protection Programs (AAHRPP). This new entity was founded by PRIM&R, the Association of American Medical Colleges, the Association of American Universities, the Federation of American Societies for Experimental Biology, and similar groups.[45] Like the accreditation process of the Joint Commission for Accreditation of Health Care Organizations and the one for laboratory animals (discussed below), the AAHRPP accreditation will be voluntary, supported by fees paid by the institutions being surveyed for accreditation, and good for three years.[46] The accreditation standards are being pilot tested on the intramural IRBs at the NIH and a few volunteer institutions, after which they will be adjusted, as necessary, and offered to other institutions.[47]

Human Stem Cells

■ New Eligibility Guidelines

Research involving human pluripotent stem cells has been an area of significant contro-

versy in recent years, and within the past year the controversy has intensified. Primarily at issue is the politically charged question of whether federal funds should be used to support research involving stem cells derived from human embryos. On August 9, 2001, President Bush announced that although his administration would allow federal funds to be used for research involving human embryonic stem cells, there would be significant limitations on such research. Specifically, President Bush announced that only those stem cells for which the derivation process had begun before August 9, 2001, the date of his announcement, were eligible to be used in projects supported with federal funds.[48] In other words, no stem cell lines derived after August 9 could be used in projects supported with federal funds. In addition, President Bush specified that federal funds could be used for stem cell research only if (a) the embryonic stem cells were derived from an embryo that had been created for reproductive purposes, (b) the embryo was no longer needed for that purpose, (c) the embryo was obtained with the informed consent of the donor, and (d) the consent was obtained without offering any financial inducements.[49] Release of the Bush administration guidelines has resulted in several significant recent developments.

■ NIH Implementation

After the announcement of President Bush's eligibility guidelines, the NIH began the process of developing a web-based Human Embryonic Stem Cell Registry that would list the stem cell lines that could be used in projects supported with federal funds. When the NIH posted its Human Embryonic Stem Cell Registry on November 7, 2001, it also explained that to list a stem cell line on the registry, a supplier must provide the NIH written assurance that the stem cells meet the President's eligibility criteria.[50] That same day, the NIH provided guidance to scientists preparing applications for funding of research involving approved stem cell lines.[51] Among the requirements is that the stem cell line to be used must be identified. Applicants who are unable to identify a specific stem cell line must promise to use an approved line and must provide the requisite information to the NIH before the initial scientific review of their application.

After the new policy concerning research involving human embryonic stem cells was announced, the NIH withdrew those sections of the previously published NIH Guidelines for Research Using Human Pluripotent Stem Cells "that pertain to research involving human pluripotent stem cells derived from human embryos."[52] The Bush Administration's eligibility criteria supersede those of the Clinton Administration.

The previous Guidelines, however, were not repealed in their entirety. The section addressing stem cells derived from human *fetal tissue* (technically referred to as human embryonic germ cells) remains in effect. When seeking NIH funding for research with fetal stem cells, an institution must provide (1) an assurance that the cells were derived in accordance with the Guidelines and applicable statutes, (2) a sample consent form, (3) an abstract of the scientific protocol used to derive the stem cells, (4) documentation of IRB approval, (5) an assurance that the cells will be obtained either through a donation or with reimbursement that does not exceed the reasonable costs of their transportation, processing, preservation, quality control and storage, (6) the title of the proposed project, (7) an assurance that the research is not of a prohibited nature, and (8) the principal investigator's consent to the disclosure of the information submitted to the extent necessary for public review and oversight.[53]

■ Licensing Issues

On September 5, 2001, the NIH entered into a memorandum of understanding (MOU) with the WiCell Research Institute, a nonprofit organization associated with the University of Wisconsin through the Wisconsin Alumni Research Foundation.[54] Under the terms of the MOU, WiCell agreed to make available to the NIH five of its stem cell lines that meet the Bush administration eligibility criteria. The

WiCell lines may be used only for education and noncommercial research. The MOU expressly prohibits use of the cells for diagnostic or therapeutic purposes.[55] Moreover, the NIH must certify annually that its research is being conducted in accordance with applicable laws, regulations, and guidelines.[56] Individual NIH laboratories can use the WiCell stem cells by signing what is referred to in the MOU as a "Simple Letter Agreement."[57] WiCell will retain the commercial rights to its stem cell lines and will be reimbursed its handling and distribution expenses.[58]

WiCell also agreed to make its stem cell lines available under the same terms offered to the NIH to nonprofit institutions that receive NIH funding. The NIH recipient, however, must enter into its own MOU with WiCell.[59] Once the MOU is signed, the institution's principal investigator may obtain the stem cells by signing the "Simple Letter Agreement." Entering into a MOU with WiCell also permits an institution to use other eligible stem cell lines covered by the same patent. As the NIH has explained: [60]

> Not only does WiCell own the specific stem cell lines derived by the University of Wisconsin, it also holds a U.S. patent for human embryonic stem cells of this type and a process for deriving them that may encompass similar lines made by other sources. The WiCell MOU provides investigators permission to use the Wisconsin stem cell lines as well as permission to use those of other stem cell sources that are covered by this patent. As a condition for the use of these patent rights, WiCell requires that you not receive stem cells from other sources under terms more "onerous" to you (i.e. more advantageous to the source) than those provided to WiCell in their MOU unless those other derivers have a license agreement with WiCell that would specifically permit such additional terms.

A similar MOU between the PHS and ES Cell International Pte. Ltd. was signed on April 2, 2002.[61]

■ Scope Of New Stem Cell Guidelines

While assessing how to implement the Bush Administration's stem cell guidelines, the NIH suspended funding for research involving human embryonic stem cells.[62] The suspension notice explained that the NIH construed the President's restrictions on the use of federal funds for embryonic stem cell research to include both direct and indirect costs.[63]

It is likely that some institutions will decide to conduct embryonic stem cell research on "unapproved" stem cell lines using only private funding. One way to carry out such a program would be to conduct the research at a laboratory supported exclusively by nonfederal funds, but beyond that, institutions have wondered how far "removed"—physically, organizationally, and financially—privately funded stem cell research would have to be from the institution's federally supported research infrastructure. On March 29, 2002, the NIH issued answers to frequently asked questions on this subject, explaining that (a) all direct costs of such research "must be charged only to non-Federal sources of funding" and (b) all indirect costs (facilities and administrative costs) must be excluded from the federal share of the organized research cost base.[64] Thus, the institution must have a method for consistently allocating all costs (including, for example, personnel, travel, equipment, and supplies) to a nonfederal source. Moreover, the institution must be able to demonstrate that no indirect (facilities and administrative) costs allocable to the research are included in the rates used to charge indirect costs to federally funded research.[65]

Laboratory Animals

The federal requirements for the care and use of laboratory animals are set out in the Animal Welfare Act (AWA)[66] and its implementing regulations,[67] which are administered by the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS).[68] Other requirements that apply to PHS-funded research are administered by the NIH's Office of Laboratory Animal Welfare (OLAW) (a remainder component of the former OPRR).

The AWA and its implementing regulations apply to "animals," defined as "any live or dead dog, cat, nonhuman primate, guinea pig, hamster, rabbit, or any other warmblooded ani-

mal" being used or intended for use in research or experimentation.[69] (Although the regulations currently do not apply to rats, mice, or birds bred for use in research,[70] APHIS settled a lawsuit that required it to initiate a rulemaking on the regulation of rats, mice, and birds under the AWA.[71]) Among the areas covered in the implementing regulations are the size of animal cages (for each species), food supply and containers, sanitation, ventilation, and access to veterinary care. In addition, each facility must have available an adequate number of employees with sufficient training to ensure that laboratory animals are maintained in accordance with the applicable regulations.[72]

All facilities that use live animals in research (whether or not they receive federal funding) must register with the USDA and must agree to comply with the AWA regulations.[73] Each research facility must establish an Institutional Animal Care and Use Committee (IACUC) to monitor the facility's animal program, facilities, and research procedures.[74] The IACUC must evaluate, at least once every six months, the research facility's program for humane care and use of animals, using the APHIS regulations as a basis for its review.[75] The IACUC must also inspect the institution's research and animal housing facilities at least once every six months.[76] In addition, each research facility registered under the AWA must submit an annual report, signed and certified by an institutional official, covering the research program for the previous fiscal year. The report must demonstrate either that the facility adhered to the AWA regulations or that any deviation was justified by the principal investigator and approved by the IACUC before experimentation.[77]

APHIS has adopted an aggressive, two-pronged, approach to enforcing the AWA. If APHIS agents believe that a noncompliant institution is genuinely interested in improving animal conditions, APHIS imposes what it calls "innovative penalties." These permit the institution to invest part or all of the monetary penalties in facility improvements, employee training, research on animal health and welfare issues, or "other initiatives to improve animal well-being."[78] When institutions do not appear to have a genuine interest in improving animal conditions, or if animals are suffering or dying from neglect, APHIS may impose significant monetary penalties, confiscate the institution's animals for relocation to another facility or, in dire situations, euthanize animals that appear to be suffering irreparably.[79]

In addition to the AWA regulations administered by APHIS, institutions that receive funding from the PHS (including the NIH) must comply with the *PHS Policy on Humane Care and Use of Laboratory Animals*.[80] This policy requires certification of IACUC approval as part of the PHS grant application whenever animal studies are involved. The institution also must maintain an approved Animal Welfare Assurance on file with OLAW.[81] Importantly, the PHS Policy applies to PHS-funded research involving live, *vertebrate* animals, a broader category of animals than covered by the AWA regulations.[82]

Compliance with the PHS Policy is generally achieved through the institutional animal care and use program described in the Animal Welfare Assurance. Assurances must be approved by OLAW before PHS funds will be released for research activities involving laboratory animals.[83] OLAW conducts site visits at institutions in response to alleged noncompliance with the PHS Policy.[84] Possible sanctions for continued noncompliance range from exclusion of individual projects from an approved assurance to withdrawal of the approval of the institution's assurance.[85] PHS funds may not be used for animal-related activities without an approved assurance.[86]

Employee health is another important component of an animal research program.[87] A good occupational health program includes preplacement and periodic medical examinations, training in animal care and appropriate research procedures (including use of protective equipment and clothing), and prompt treatment of injuries or illnesses that may be related to laboratory animals or that could in-

fect the animals.[88] Helpful guidance may be found in *Occupational Health and Safety in the Care and Use of Laboratory Animals,* published by the National Academy of Sciences.[89]

Many research institutions confirm compliance with animal welfare requirements through accreditation by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).[90] The AAALAC accreditation program consists of a voluntary, comprehensive evaluation of an institution's animal welfare program. If granted, the accreditation is valid for three years, after which the institution must be reevaluated.

Biosafety

The intensified concern over bioterrorism in the aftermath of September 11 and the subsequent anthrax mail attacks has caused Congress, federal regulators, and federal law enforcement authorities to increase their scrutiny of potential sources of infectious materials. One example of that increased scrutiny is the recent announcement that the HHS IG has initiated a series of comprehensive biosafety audits at a number of academic biomedical research laboratories. The HHS audits and the generally increased level of federal scrutiny are bringing into focus the need for research institutions to include in their compliance programs procedures to ensure that they are operating in compliance with the numerous statutes and regulations that govern the use, handling and transportation of etiologic (infectious) agents (i.e., viable microorganisms and toxins that may cause human disease).[91]

Although there are numerous regulations governing laboratory security and safety, this PAPER focuses *primarily* on regulations of the Centers for Disease Control and Prevention that are at the center of the current debate concerning the safety of university and commercial laboratories. Some of the other relevant regulations include Occupational Safety and Health Administration rules on occupational exposure to hazardous chemicals in laboratories[92] and occupational exposure to bloodborne pathogens[93] and the *NIH Guidelines for Research Involving Recombinant DNA Molecules.*[94] There are also both federal and state regulations pertaining to radiation safety.[95]

■ CDC Regulations

The Antiterrorism and Effective Death Penalty Act of 1996 required the HHS to promulgate regulations that would, among other things, list the biological agents that pose a significant risk to the public's health and safety, establish and enforce safety procedures governing the transportation of those agents, implement safeguards to prevent unauthorized access, and ensure the appropriate availability of regulated agents for research, educational, and other legitimate purposes.[96] The HHS delegated these responsibilities to the CDC, which amended existing regulations on the handling of etiologic agents by adding provisions governing the transfer and receipt of certain "select" agents.[97]

Over 30 viruses, bacteria, rickettsiae, fungi, and toxins are designated as "select agents."[98] To transfer or receive a select agent lawfully, a facility must register as an approved entity or be approved by the CDC as being equipped to handle select agents at Biosafety Levels 2, 3, or 4, depending on the agent being handled.[99] (Biosafety levels are graded according to the amount of protection provided, with Level 4 being the safest.) To become a registered facility, an applicant must provide sufficient information to demonstrate that it is equipped to handle select agents at the appropriate biosafety levels and permit federal inspections.[100] Once approved, the facility receives a unique registration number and may be subject to further inspections to ensure that it maintains the level of safety required for handling select agents.[101]

Before transferring any select agent, both the requesting facility and the transferring facility must complete a CDC Form EA-101, providing detailed information about both the facility and the agent being transferred.[102] The form must be signed by both the transferor facility and the requestor, as well as by the responsible facility officials from both entities.[103]

Both facilities must maintain the form for a period of five years after the date of shipment, or for five years after the select agents are consumed or disposed of, whichever is longer.[104] Facilities also must produce the form when requested by federal and authorized local law enforcement personnel, authorized agents of the Secretary of the HHS, and officials of the registering entity.[105]

An additional pretransfer requirement for select agents is that the transferor's responsible facility official must verify that the requesting facility's registration complies with the CDC regulations.[106] If verification cannot be obtained or if the transferring facility suspects that any of the information received is incorrect, the facility must notify the CDC.[107] Only after the proper completion of all forms and verification of the requesting facility's registration may the transfer of a select agent occur. Finally, the CDC regulations require certain verification of delivery to ensure that a select agent arrives at the proper destination in a timely manner.[108]

Multiple packaging requirements apply to the shipment of etiologic agents (including "select agents").[109] For example, biological materials that may be infectious must be packaged in a prescribed manner to prevent leaks and to ensure that the material can withstand shocks, temperature and pressure changes, and other stresses.[110] They must also carry warning labels of a specific size and design.[111]

Clinical laboratories certified under the Clinical Laboratories Improvement Amendments of 1988[112] that use select agents for diagnostic, reference, verification, or proficiency testing purposes are exempt from the CDC regulations.[113] In addition, a select agent is exempt from the regulations if it is (1) "part of a clinical specimen intended for diagnostic, reference, or verification purposes," (2) a small amount of toxin that is used for legitimate medical purposes or biomedical research or a toxin that has been inactivated for use as a vaccine or otherwise detoxified for use in biomedical research procedures, or (3) an exempt strain as specified by the CDC.[114]

■ USA PATRIOT Act

Another source of biosafety requirements is the recently enacted Uniting and Strengthening America by Providing Appropriate Tools Required To Intercept and Obstruct Terrorism (USA PATRIOT) Act of 2001.[115] The Act criminalizes, with limited exceptions, the possession of any biological agent, toxin, or delivery system "of a type or in a quantity that, under the circumstances, is not reasonably justified by a prophylactic, protective, bona fide research, or other peaceful purpose."[116] That language is unfortunately rather vague in that it fails to define either a threshold quantity or the types of agent, toxin, or delivery system necessary to trigger the criminal provision. Individuals convicted of unlawfully possessing toxic substances are subject to fines and imprisonment for up to 10 years.[117]

The PATRIOT Act also prohibits "restricted persons" from transporting, shipping, or possessing "select agents."[118] "Restricted persons" include individuals under indictment for or convicted of a crime punishable by imprisonment for more than one year, fugitives from justice, unlawful users of controlled substances, aliens illegally in the United States, individuals adjudicated mentally defective, individuals who have been dishonorably discharged from the U.S. Armed Services, and aliens who are nationals of countries that are designated as supporting acts of international terrorism.[119] Violations of this prohibition may result in fines and imprisonment.[120]

Compliance with the "restricted persons" element of the PATRIOT Act could prove especially problematic for research institutions because in many cases they may be unequipped to obtain the information necessary to ensure compliance with the Act's restrictions. For example, most colleges and universities do not test their faculty and students for the use of controlled substances.

■ Physical Safeguards

A further biosafety requirement for research institutions is the implementation of physical security measures to prevent unauthorized

access to laboratories handling etiologic agents, as well as to research information stored in such laboratories. This presumably includes electronic research data pertaining to experiments involving etiologic agents. Some guidelines on physical security for laboratories are provided in a CDC publication entitled *Biosafety in Microbiological and Biomedical Laboratories.*[121] These guidelines, however, are general, thereby leaving significant discretion in determining what the appropriate security measures might be.

Research institutions continue to face uncertainties regarding biosafety. The 2002 Department of Defense Appropriations Act had contained language addressing biosafety. Although deleted from the final bill, the proposed language appears likely to serve as a basis for future legislation. For example, the HHS would be required to review and revise the select agent list biennially and to issue regulations governing the possession and use of select agents, including restricting access to those individuals who "need" to handle or use select agents and requiring background checks on those individuals. Institutions whose laboratories handle biological agents should monitor future developments regarding biosafety and participate in the rulemaking process.

Financial Conflicts Of Interest

The increasing relationships between the pharmaceutical industry on the one hand, and clinical researchers and academic institutions on the other, have caused concern—both within and outside the academic community—for over a decade. The primary concern is whether research directions or findings may be unduly influenced by the investigators' financial interests in commercial entities or in the product or process being evaluated. Academic institutions also worry that a professor's commercial interests might adversely affect the rights of students to choose their own research topics and to publish their findings. The NIH first proposed conflict of interest rules in 1989.[122] They were severely criticized as too draconian and were subsequently abandoned. After considerable deliberation, regulations were finally issued in 1995 by the PHS[123] and in 1998 by the FDA.[124] The regulations set no absolute limits on the nature or extent of interests researchers may have in commercial entities. Instead, the PHS requires institutions to "manage, reduce or eliminate" any significant financial conflicts of interest disclosed by researchers,[125] and the FDA simply requires that all such conflicts be reported after the research has been completed when the data are submitted in support of an application for marketing.[126]

■ PHS Regulations

The PHS regulations concerning the "Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding is Sought"[127] require institutions to "[m]aintain an appropriate written, enforced policy on conflict of interest."[128] The policy must include procedures under which "investigators" disclose to a designated institutional official their "significant financial interests" that "may reasonably appear to be affected by" their PHS-funded research.[129]

Under the regulations, "*investigators*" are defined as "the principal investigator and any other person who is responsible for the design, conduct, or reporting of research funded by PHS, or proposed for such funding."[130] The term also includes the investigator's spouse and dependent children.[131] "*Significant financial interest*" is "anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interests (e.g., stocks, stock options or other ownership interest); and intellectual property rights (e.g., patents, copyrights and royalties from such rights)."[132] The term does *not* include (a) salary, royalties, or other payments from the applicant institution, (b) any ownership interest in an institution applying for an Small Business Innovation Research Program grant, (c) income from seminars, lectures or teaching engagements sponsored by Government or nonprofit entities, (d) income from service on advisory or re-

view committees for Government or nonprofit entities, (e) equity interests that, when aggregated for the investigator and the investigator's spouse and dependent children, do not exceed a fair market value of $10,000 per year or 5% ownership interest in any single entity, or (f) salary, royalties, or other payments (aggregated for the investigator, the spouse, and dependent children) that are not expected to exceed $10,000 in the next 12 months.[133]

A designated institutional official or committee must review the investigators' disclosures and take appropriate action to "manage, reduce, or eliminate" any conflicts of interest that could directly and significantly affect the design, conduct, or reporting of the PHS-funded research.[134] Examples of methods that may be used to "manage" financial of conflicts of interest include public disclosure of the conflict, independent monitoring of the research, divestiture of financial interests, and modification of the research plan.[135]

The PHS regulations do not prescribe a format for investigator disclosures or identify a specific institutional office to administer the conflict of interest policy, nor do they address whether or which financial conflicts of interest must be disclosed to potential research volunteers during the consent process. There are no rules about situations in which it is the institution, alone or in addition to the investigator, that has the conflict of interest. Finally, the PHS regulations do not address the possible role of IRBs in the management of conflicts of interest or the conflicts of IRB members, perhaps because the IRB regulations prohibit IRB members from participating in the review of any project in which they have a conflict of interest, other than to provide information requested by the IRB.[136]

■ FDA Regulations

The FDA has promulgated its own conflict of interest regulations[137] that apply to entities submitting data in support of an application for marketing a human drug, biological product, or device.[138] Under the FDA regulations, an applicant must certify on an FDA form (FDA 3454) that the clinical investigators associated with a study have no financial arrangement with the study sponsor affected by the outcome of the study.[139] If unable to provide such a certification for a particular investigator, the sponsor/applicant must disclose on another FDA form (FDA 3455) (1) the equity or other financial interest of any investigator in the sponsor, (2) the proprietary or royalty interest of any investigator in the product tested, and (3) any significant payment of other sorts by the sponsor to an investigator.[140]

■ Recent Developments

In late 2000, both the Journal of the American Medical Association[141] and the New England Journal of Medicine[142] devoted major portions of their publications to financial conflicts of interest. Among the topics covered by the journals were how investigators' conflicts of interest might compromise the safety of human research subjects and the wide variation among academic institutions in their conflicts of interest policies and practices. It is no surprise, therefore, that the management of financial conflicts of interest continues to be an important issue for the research community.

Given the continuing controversy, the HHS held a well publicized conference in August 2000 on regulating financial conflicts of interest and protecting human subjects. Participants at the meeting voiced concern that existing policies do not address issues such as equity holdings by IRB members and the institutions themselves, a special concern when human subjects are involved. Based predominantly on presentations made at the conference and on comments received later, the HHS issued "draft interim guidance" on January 10, 2001, entitled "Issues for Institutions, Clinical Investigators, and IRBs To Consider When Dealing With Issues of Financial Interests and Human Subject Protection."[143]

The draft interim guidance, which applies to both federally funded and nonfederally funded clinical research, was issued with the express intent of assisting IRBs, clinical in-

vestigators, and institutions in carrying out their responsibilities for the protection of human subjects.[144] The document suggests that agreements between investigators and a private sponsor should be reviewed by a conflict of interest committee or equivalent body.[145] If a potential conflict cannot be eliminated, the committee's determination on managing the conflict should be shared with the IRB for consideration during its review of the protocol.[146] The IRB should consider whether the conflict of interest should be disclosed to potential subjects on the consent form.[147] In addition, IRBs should consider identifying the source of funding for the study, and describing the payment arrangements for investigators, in the consent form "whenever that information is considered to be material to the potential subjects' decision-making process."[148]

With respect to the IRB members, the draft interim guidance suggests that the IRB chair should ask members at each meeting about potential conflicts they may have in any protocol that the IRB is going to review.[149] The IRB also should implement "clear procedures" for the recusal of members with an actual or perceived conflict.[150] The draft interim guidance notes that many IRBs remind their members of such polices at the beginning of each meeting and record any recusals in meeting minutes.[151]

Significantly, the draft interim guidance also emphasizes that institutions must manage their own conflicts of interest, as well as those of their employees. For example, if an institution accepts a principal equity interest in a biotechnology company as part of a cooperative venture to commercialize a new product, the institution "should carefully consider" whether a clinical trial to evaluate safety and efficacy should be performed elsewhere.[152] The draft provides as follows:[153]

> The financial interest of the institution in the successful outcome of the trial could directly influence the conduct of the trial, including the enrollment of subjects, adverse event reporting or evaluation of efficacy data. In such cases, the integrity of the research, as well as the integrity of the institution and its corporate partner, and well-being of the research participants, may be best protected by having the clinical trial performed and evaluated by independent investigators at sites that do not have a financial stake in the outcome of the trial, or carried out at the institution but with special safeguards to maximally protect the scientific integrity of the study and the research participants.

The guidance further provides that any financial relationships that the institution has with the commercial sponsor of a study should be documented, and submitted to the IRB as part of its review.[154]

Public comments responding to the draft interim guidance have emphasized the additional burdens that the guidance would impose on IRBs. The FDA, for example, commented that responsibility for managing financial conflicts of interest should not be placed on IRBs, which are already over-burdened and not appropriately constituted to perform this task.[155] The FDA suggested that a conflicts of interest committee should be responsible for the review, management, or elimination of financial conflicts of interest.[156] IRBs could receive the final action of the committee for the sole purpose of determining whether further action is necessary, such as adding information to the consent form or placing further restrictions on the study. [157]

Informed consent was also a significant topic of several comments. The Association of American Medical Colleges (AAMC) suggested that the draft interim guidance may be too lenient in permitting IRBs to determine when disclosures should be made to potential research subjects. Instead, the AAMC stated that disclosure "should be required to the IRB and to prospective subjects during the consent process of *all financial relationships* of the investigator(s) with the study's sponsor or with a provider of materials that are to be evaluated in the study" because all such arrangements are material to a potential subject's decisionmaking process.[158]

Another group of comments expressed concern about the prescriptive nature of the guidance.[159] The Association of American Universities' Council on Government Relations and

the National Association of State Universities and Land Grant Colleges contended that "substantive new responsibilities, such as those described in the draft interim guidance for IRBs, are too extensive to be announced as guidance, in draft or otherwise," and must meet the notice and comment requirements of the Administrative Procedure Act.[160]

The draft interim guidance has yet to be finalized and the topic of financial conflicts of interest continues to be of significant interest to the research community. For example, the Association of American Medical Colleges, recently published a report suggesting a comprehensive disclosure and oversight system that would involve reviewing all "significant financial interests in human subjects research," whether or not the research is publicly funded.[161] The report, however, addresses only those conflicts of interest associated with individual faculty, staff, employees, students, fellows, and trainees; it does not reach institutional conflicts of interest—a topic that will apparently be covered by a forthcoming report.[162]

The AAMC Report sets forth six core principles for a conflicts of interest policy. First there should be a rebuttable presumption that any individual with a conflict of interest should be precluded from engaging in the affected research.[163] Second, only in compelling circumstances should the presumption be set aside.[164] Third, an effective policy must include meaningful reporting requirements and a review of those reports by a conflicts of interest committee before IRB review.[165] Fourth, policies should be "comprehensive, unambiguous, well-publicized, consistently applied, and enforced through effective sanctions."[166] Fifth, whenever compelling circumstances warrant allowing an individual with a conflict of interest to conduct human subjects research, the institution must engage in "rigorous, effective, and disinterested" monitoring of both the conflict and the research.[167] Sixth, an effective policy should enhance the ability of individuals engaged in human subjects research to understand and apply the relevant guidelines.[168]

Meanwhile, the current regulations remain in effect and set the compliance standard. Institutions would be well advised to review their current policies and consider what revisions would be necessary to bring them within best practices in this area. Financial conflicts of interest—of the researcher, the IRB, or the institution—pose risks to an institution, especially when the affected research involves human subjects. Failure to manage them adequately could result in adverse administrative actions, including the suspension of some of an institution's research activities, if it is determined that the conflict compromised the safety of human subjects. Worse, if an unexpected death occurs in research, the press and the public may assume a causal connection with financial interests on the part of the investigator, whether or not there is a factual basis for that assumption.

Research Misconduct

Institutions conducting biomedical research with Government funds are subject to statutes, regulations, and policies addressing research integrity or scientific "misconduct."[169] These rules apply not only to the conduct and reporting of research but also to the application for funds, and they generally require that institutions develop policies for responding to allegations of research misconduct.

The past few years have witnessed a slight rise in allegations of research misconduct. In its 2000 Annual Report on Possible Research Misconduct, the HHS Office of Research Integrity ("ORI") indicated that 82 institutions reported misconduct allegations involving PHS-funded research, compared with 72 in 1999 and 67 in 1998.[170] Of 103 new allegations, 37 involved fabrication, 24 involved falsification, 19 involved plagiarism, and 23 concerned "other" issues.[171] Historically, however, only a small portion of such allegations result in a finding of scientific misconduct.[172]

■ PHS Regulations

Scientific or research "misconduct," as defined by the regulations, includes "fabrication,

falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research."[173] It does not include "honest error or honest differences in interpretations or judgments of data."[174] (A similar definition is used in the National Science Foundation regulations, which track the PHS rules.[175]) For historical reasons, the definition does not include violation of regulations uniquely relevant to research, such as those governing the protection of human subjects or the care and use of laboratory animals.[176] Nevertheless, many academic institutions do include those matters within their definition of scientific misconduct, while others deal with them under the "serious deviations" element of the definition. (A few have discovered to their dismay that they have no institutional policies and procedures for dealing with serious violations of the IRB regulations.)

The PHS regulations require a two-stage response to allegations of scientific misconduct: (1) an inquiry to determine whether a formal investigation is warranted, and (2) an investigation to determine whether misconduct has occurred and, if so, by whom.[177] Individuals against whom allegations are made must be provided "confidential treatment to the maximum extent possible, a prompt and thorough investigation, and an opportunity to comment on allegations and findings of the inquiry and/or the investigation."[178] Their comments should be made part of the record.[179] Written reports must include a description of the evidence reviewed, summaries (or transcripts) of interviews, and the findings and conclusion of the inquiry or investigative committee.[180] Summaries of interviews should be prepared and provided to the individuals who were interviewed for correction or comment.[181] (Many institutions use interview summaries for the inquiry phase and transcripts for the formal investigation.)

The regulations further require institutions to (a) secure expert consultants, as needed, for "a thorough and authoritative evaluation of the relevant evidence in any inquiry or investigation," (b) take precautions against conflicts of interest, and (c) prepare and maintain documentation to support the findings of the inquiry or investigation.[182] In addition, institutions must undertake "diligent efforts" both to restore the reputation of individuals found not to have engaged in scientific misconduct and to protect from retaliation those who made allegations in good faith.[183] Institutions must take interim administrative actions, as necessary, to protect public funds, impose appropriate sanctions if misconduct is confirmed, and report to the ORI or the NSF the final outcome of investigations.[184] No report is required following an inquiry unless it concludes that an investigation is warranted. At that point, the ORI must be notified.[185] During the inquiry and investigation, if there is any "reasonable indication of possible criminal violations," the institution must notify the ORI within 24 hours and the ORI, in turn, will notify the HHS OIG.[186] The ORI has developed model policies and procedures to assist institutions in responding to allegations of scientific misconduct and conducting inquiries and investigations as warranted.[187]

The HHS recently assigned responsibility for scientific misconduct investigations to the HHS OIG, following the example of the NSF and allowing the ORI to focus more on education, research, and the prevention of scientific misconduct.[188] A finding that a faculty member, graduate student, or technician has committed scientific misconduct can result in the imposition of administrative remedies or legal sanctions against the individual and the institution. Such actions may include (1) *administrative remedies*, such as the retraction or correction of publications, recoupment of Government funds, requirements for supervision and prior approval of research, special restrictions on research activities, suspension of ongoing research, suspension or termination of an award, or suspension or debarment of the individual, (2) *civil monetary penalties*, such as treble damages under the civil provisions of the False Claims Act or penalties imposed under the Program Fraud Civil Remedies Act, or (3) *criminal sanctions*, such as those applied under the criminal provisions of the False Claims Act or the false statements statute.[189]

■ Government-Wide Policy

Recognizing the need for consistency in this area, on December 6, 2000, the White House Office of Science and Technology Policy (OSTP)[190] issued a Government-wide "Federal Policy on Research Misconduct" that agencies were supposed to adopt and implement by December 6, 2001.[191] The Research Misconduct Policy would apply to *all federally funded research and proposals,* including research performed under grants, cooperative agreements, and contracts. "Research" is defined broadly to include "all basic, applied, and demonstration research in all fields of science, engineering, and mathematics."[192] Agencies may implement the policy by revising their existing regulations, promulgating new regulations, or developing "administrative mechanisms" if formal rulemaking is not required.[193] Thus far, HHS has not taken formal action to adopt the federal policy.

The most significant aspect of the Government-wide policy is that it slightly modifies the PHS definition of scientific "misconduct" by adding "reviewing research" and deleting the troublesome (to many) "serious deviation" clause of the PHS definition.[194] It also defines key terms. "Fabrication" is defined as "making up data or results and recording or reporting them."[195] "Falsification" is defined as "manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record including biological materials."[196] (The "research record" includes, for example, the research proposal, laboratory records, progress reports, abstracts, theses, oral presentations, internal reports, and journal articles.[197]) "Plagiarism" is defined as "the appropriation of another person's ideas, processes, results, or words without giving appropriate credit."[198] As under the existing PHS regulations, authorship disputes are not covered unless the dispute involves allegations of plagiarism.[199] In omitting the controversial "serious deviation from accepted practices" clause (currently in the PHS definition of "misconduct"), the OSTP explained that "other improper practices" are more appropriately addressed by other institutional policies and agency rules, just as violations of the rules for protecting human subjects or animals in research, the misallocation of funds, sexual harassment, or discrimination are currently handled by other HHS offices.[200]

As under current PHS and NSF rules, "research misconduct" will not encompass "honest error or differences of opinion."[201] The preamble to the Government-wide policy emphasizes that the exclusion of honest error and differences of opinion is not intended to create a separate element of proof. In other words, the agency is not required to prove that an action was not the result of honest error or different interpretations or judgments of data.[202] Decisions of the HHS Departmental Review Board, by contrast, have held the opposite.[203]

Although the current HHS and NSF regulations are silent with respect to the standard of proof, the Government-wide policy applies a "preponderance of the evidence" standard.[204] This standard is used in lieu of a more stringent standard, such as "clear and convincing evidence," because the preponderance of the evidence standard is used in most civil fraud cases and federal administrative proceedings, including debarment.[205] Institutions may adopt a more stringent standard of proof for their own purposes, but they must apply the preponderance of the evidence standard in their deliberations and findings to be reported to the Federal Government.[206]

Similar to existing PHS regulations, the Government-wide policy establishes specific points in the institution's internal review process that trigger an obligation to report to the funding agency, including when public health or safety is at risk, the agency resources are threatened, or there is reasonable indication of possible violations of civil or criminal law.[207] Moreover, as in the current PHS regulations, the Government-wide policy requires institutions to establish procedures to ensure the fair treatment of both informants and the subjects of misconduct allegations. For informants, the policy adds that institutions must adopt pro-

cedures for a fair and objective examination and resolution of allegations of retaliation;[208] for the accused, the policy requires institutions to establish procedures to avoid unwarranted disruption of ongoing research.[209]

The Government-wide policy also eliminates the time frames in which the inquiry and investigation must be concluded. Current PHS regulations require that inquiries be concluded, if possible, within 60 days.[210] Investigations must be initiated within 30 days after completion of the inquiry and completed, if possible, within 120 days thereafter.[211] No such time frames are in the new policy because most institutions and especially the ORI found them impossible to meet.

At the time of this writing, the ORI website indicated that PHS-funded institutions should continue to apply the current PHS regulations until the HHS formally implements the Government-wide policy through revised regulations.[212] Once implemented, the Government-wide policy will provide a more uniform approach to compliance across federal departments and agencies.

Data Privacy

Patients' rights in general, and more specifically the privacy of medical records, have recently been an area of significant public policy debate. Although covered entities are not required to comply until April 14, 2003, privacy regulations promulgated by the HHS[213] under the authority of the Health Insurance Portability and Accountability Act of 1996 (HIPAA)[214] are already having a significant impact on the research activities of academic medical centers, which will likely be considered covered health care providers[215] and therefore subject to the regulations. The primary focus of the HIPAA privacy regulations is to prevent unauthorized uses and disclosures of individually identifiable health information. "Individually identifiable health information" means health-related information created or received by a covered entity that (a) concerns (1) the past, present, or future physical or mental health or condition of an individual, (2) the provision of health care to a individual, or (3) the past, present, or future payments for the provision of health care to an individual *and* (b) identifies the individual or with respect to which there is a reasonable basis to believe the information can be used to identify the individual.[216]

From the perspective of research compliance, the HIPAA privacy regulations effectively add a new layer of requirements to the federal Common Rule requirements pertaining to research involving human subjects, which were discussed earlier in this PAPER. Specifically, the HIPAA privacy regulations augment the Common Rule by imposing additional authorization and waiver of authorization requirements that are intended to focus IRBs' attention on the protection of individuals' privacy interests.

■ Authorization & Waiver

As a general rule, the HIPAA privacy regulations prohibit covered health care providers from using or disclosing identifiable health information for research purposes, whether as part of a review of existing medical records or a clinical trial, without written authorization or a waiver of authorization from an IRB or a privacy board. This authorization is distinct and contains different elements from the informed consent required by the Common Rule. The HIPAA privacy regulations are also broader than the Common Rule in that they reach privately funded research and research involving deceased individuals.

(a) *Authorization for research uses and disclosures not involving treatment*—Under the HIPAA privacy regulations, medical centers generally must obtain an individual's authorization to use or disclose a patient's protected health information for "research" purposes—defined broadly as any "systematic investigation" designed to develop or contribute to "generalizable knowledge."[217] Under the regulations, "protected health information" includes (with limited exceptions) individually identifiable health information that is (1) transmitted by electronic media, (2) maintained in an electronic media, or (3) transmitted or maintained in any other format.[218] An authorization for

reviews of existing medical records and for other uses and disclosures of protected health information created or collected for purposes other than research involving treatment must comply not only with the HIPAA privacy regulations, but also with any applicable state laws, unless an IRB or privacy board grants a waiver.

As noted above, this authorization requirement is distinct from, and in addition to, Common Rule requirements relating to informed consent of a subject to participate in a research protocol. The authorization requirement also is separate from the related HIPAA requirement that medical centers obtain "consent" to use or disclose protected health information for treatment, payment, and health care operations purposes.[219] With the exception of authorizations for research involving treatment (discussed below), an authorization to use or disclose protected health information for research purposes generally may not be combined in the same document with a HIPAA consent or an informed consent.[220] In addition, it should be noted that a health care provider generally may not condition treatment on obtaining an authorization.[221]

(b) *Authorization for research that includes treatment*—When, as in the case of a clinical trial, a medical center creates or collects protected health information *for the purpose of* research that includes "treatment"—broadly defined to include any provision of health care or services, coordination or management of health care, and referrals[222]—the HIPAA privacy regulations require that an authorization to use or disclose such information incorporate all of the elements of a regular authorization and, *in addition*, (1) describe the extent to which protected health information will be used or disclosed for treatment, payment, or health care operations, (2) state whether any research information will be protected from uses or disclosures otherwise permitted by the HIPAA privacy regulations without consent or authorization, and (3) refer the individual to the medical center's consent form for treatment, payment, and health care operations and notice of privacy practices, if applicable, and state that such consent and notice are binding upon the medical center.[223] Authorizations for the use and disclosure of protected health information created for research involving treatment differ from regular authorizations in other ways as well. For example, if the research involves treatment, the authorization may be combined with a HIPAA consent.[224] Likewise, a health care provider may condition research-related treatment on obtaining an authorization.[225]

(c) *IRB or privacy board waiver of authorization*—As an alternative to obtaining an individual authorization, a medical center may seek a waiver of the authorization requirement from an IRB established in accordance with the Common Rule or from a privacy board, a new entity created by the HIPAA privacy regulations.[226] The member composition and procedural requirements for privacy boards are essentially the same as those for IRBs,[227] and either entity may grant a waiver of authorization,[228] provided that certain criteria, similar to the Common Rule criteria for the waiver of informed consent, are satisfied.[229] The reviewing board, however, must specifically determine that the scientific merit of the proposed research outweighs the risks to individual privacy—a criterion many IRBs heretofore have not considered in great depth.

The HHS indicated in guidance issued July 6, 2001, that, for purposes of the HIPAA privacy regulations, an IRB or privacy board need *not* be affiliated with the health care provider that maintains the protected health information sought to be used or accessed for research purposes.[230] Thus, a medical center is permitted under the HIPAA privacy regulations to disclose protected health information on the basis of a waiver of authorization by an external privacy board (for example, a board affiliated with a pharmaceutical manufacturer or other research sponsor). Medical centers are not, however, required to accept such third-party waivers and, in fact, should contemplate carefully all of the relevant legal and ethical implications before doing so. If a medical center chooses to rely on third-party waivers, appropriate policies and procedures should be established to guide the consideration process

(e.g., who at the medical center will review third-party waivers and from which third-party boards will the medical center accept—or not accept—waivers). For research conducted under the Common Rule, a third-party waiver of Authorization may not be particularly useful, since a medical center-affiliated IRB may be required to review the research protocol anyway.

■ Recruitment Of Research Subjects

The HIPAA privacy regulations will have a significant impact on the recruitment of clinical trial and other research subjects. Under the regulations, a medical center may allow researchers to review protected health information—without authorization or waiver of authorization—"as necessary to prepare a research protocol or for similar purposes preparatory to research."[231] The apparent purpose of this exception to the authorization requirement is to enable researchers to use existing patient medical records to identify sources of prospective subjects for participation in research protocols. However, the medical center may provide a researcher access to its records under this exception *only* if the researcher represents that no protected health information will be removed and that access to the information is necessary for research purposes.[232] While the scope of this exception is uncertain, the HHS has made clear that the researcher may not record or remove patient-identifiable information during the course of a preparatory review.

■ Use & Disclosure Of "De-Identified" Information

The HIPAA privacy regulations cover only the use and disclosure of protected, or individually identifiable, health information; they do not apply to "de-identified" health information.[233] Thus, a medical center may freely use or disclose de-identified patient data for research. Information may be considered "de-identified," however, only if it satisfies one of two de-identification standards. First, information may be considered "de-identified" if a statistician concludes that the risk is "very small" that the information could be used, alone or in combination with other reasonably available information, by an anticipated recipient to identify an individual who is a subject of the information. The statistician must document the methods and results of the analysis.[234] Alternatively, information is deemed "de-identified" if the medical center has no actual knowledge that the information could be used alone or in combination with other information to identify the subject of the information *and* the medical center removes from the data *all* of certain identifiers concerning the patient and the patient's employer, relatives, and household members.[235]

■ Proposed Changes

Because of the generally controversial nature of the HIPAA privacy regulations, on March 27, 2002, the HHS published a proposed modification[236] that, if finalized without alteration, will affect considerably those portions of the HIPA privacy regulations applicable to researchers. Because it is difficult to predict which of the proposed changes will be implemented, this PAPER provides only a general overview of the more significant proposed modifications.

First, the HHS has proposed to modify the requirements of the HIPPA privacy regulations concerning waivers of the obligation to obtain a research participant's authorization. The proposed modification purports to (a) make the privacy regulations' waiver requirements more consistent with the Common Rule's waiver provisions and (b) remove some of the current redundancies. Second, the HHS has proposed to modify the privacy regulations' provisions regarding authorizations to create a uniform set of requirements for all authorizations, including those for research purposes. Third, covered entities would be able to condition research-related treatment on the provision of an authorization for the use and disclosure of protected health information. Fourth, the HHS proposes to remove the additional authorization requirements that currently exist for research studies involving treatment and also to clarify the existing regulations for the purpose of allowing a research-related autho-

rization to be combined with any other type of legal permission related to the research being conducted (e.g., a consent to participate). There are also proposed modifications concerning the requirement that an authorization contain an expiration date or event, as well as revised research transition provisions (e.g., requirements applicable to research commencing before the privacy regulations' compliance date but continuing after).

NIH Proactive Compliance Site Visits

An important signal of the NIH's increased emphasis on promoting strong institutional compliance programs is its adoption of a "proactive compliance site visit" program. Among the likely rationales for the NIH's decision to implement the site visit program is the increased number of compliance-related issues being brought to the NIH's attention.[237] For example, grants-related allegations increased 37% from Fiscal Year 1999 to FY 2000 and grants-related cases handled by the NIH increased from 40% to 53% of all cases in that same period.[238]

Consequently, during FYs 2000 and 2001, personnel from the NIH Office of Extramural Research conducted site visits at 18 research institutions.[239] These site visits were viewed neither as audits nor as investigations; rather, the NIH's purpose was to assess institutional understanding of federal policies and regulations, to minimize or eliminate noncompliance, and to nurture a productive partnership between the NIH and its grantee institutions.[240] The topics covered during these visits included (1) institutional roles and responsibilities, (2) training and education, (3) financial conflicts of interest, (4) financial management of sponsored projects, (5) clinical trial data safety and monitoring, and (6) Bayh-Dole Act/invention and patent reporting.[241] Several of the site visits addressed additional topics such as clinical gene transfer research and hazardous waste disposal.[242]

In its April 2001 report on the site visits,[243] the NIH stated that the institutions visited demonstrated varying degrees of institutional oversight, but that in all cases oversight could be strengthened to minimize the risk of noncompliance. The NIH had requested that the institutions provide copies of their policies, forms, procedures, manuals, organization charts, and other materials in advance of the site visits. Some of the institutions commented that the exercise of preparing for the site visit was a valuable activity, and that the NIH's presence strengthened the culture of compliance. Some of the institutions also expressed concern regarding the cost of compliance, considering that administrative cost recovery through the indirect cost rate remains capped at 26%. Another noteworthy observation expressed in the report was the NIH's view that it perceived an "undercurrent of distrust" at the institutions, especially concerning issues pertaining to financial conflicts of interest. Moreover, the NIH observed that some faculty members are reluctant to fully disclose financial conflicts of interest for fear that the institution would use this information against them.

Perhaps the most valuable insights to be gained from the NIH's report are set forth in the sections entitled "Examples of Compliance in Action."[244] For example, the NIH cited with approval the practice of requiring concurrence by an institution's conflict of interest committee with plans to manage conflicts of interest. Once approved, the management plans are formalized in a memorandum of understanding. Another example cited by the NIH is the practice of clinical investigators' meeting regularly to review reports and address accrual, retention, protocol compliance, safety, and other trial outcomes, as appropriate. In the area of financial management, the NIH cited with approval the practice of maintaining a "Sponsored Projects Expenditure Compliance Office" to monitor charges to sponsored projects, identify questionable or inappropriate charges, and formally notify appropriate institutional officers when necessary. What each of the above examples teaches is that the NIH looks favorably on institutional efforts that promote compliance by involving both faculty and administrators in programs designed to prevent problems before they occur.

Effective Compliance Programs

This BRIEFING PAPER, together with its companion PAPER on financial and administrative compliance issues,[245] is designed to promote greater knowledge and understanding of the complex regulatory environment applicable to federally sponsored research. Knowledge is, of course, only the first step in a successful compliance program.

Thus, a common shortcoming in many institutional compliance programs noted in the earlier PAPER bears repeating here. That is the notion that people will follow the rules as soon as they are sufficiently instructed as to what the rules are. The corollary to this commonly held belief is that the "solution" to the compliance problem is better and more extensive personnel training. A successful compliance program, however, cannot be limited to education and training alone.

That is not to minimize the importance or apparent extent of ignorance of the rules and regulations. However, lack of knowledge generally is not the source of the most worrisome compliance problems, i.e., those that can lead to significant civil and even criminal penalties. As explained in the previous PAPER, the most significant research compliance problems are often the result of financial, organizational, informational, management, and cultural obstacles to compliance that plague research institutions. It is these obstacles, not mere ignorance or inadvertence, that can make it appear that an institution or its leadership has knowingly and willfully violated federal laws and regulations.

To overcome these obstacles, an institution needs to work toward developing a compliance program that has the visible support of senior institution personnel. It also needs competent compliance personnel with well-defined roles and responsibilities, clearly written policies and procedures, a thorough system of training, sufficient reporting and review mechanisms, strong enforcement mechanisms, and adequate resources. Equally important is the ability and willingness of compliance personnel to identify the cause of a persistent problem rather than simply reacting to situations as they arise. That is especially true with respect to biomedical research, where federal regulations are designed not only to safeguard public funds but also to protect the rights and well-being of research subjects and, for that matter, the public at large.

GUIDELINES

These *Guidelines* are intended to help you understand the regulatory requirements for federally sponsored research discussed in this PAPER. They are not, however, a substitute for professional representation in any specific situation.

1. Recognize that your first step in complying with regulatory requirements applicable to federally sponsored research is to *learn the rules*. Administrative personnel responsible for compliance should not rely on hearsay, assumptions, and mythology as to what the applicable rules and regulations provide.

2. Keep in mind that the regulations are not only complex, but also *far from static*. Moreover, some may vary *from agency to agency*. A compliance program must account for these differences and should include *ongoing monitoring* of regulatory and policy developments.

3. Remember that a key aspect of an effective compliance program is the *training* of personnel at all levels of the institution on the requirements of the *applicable rules* and *their responsibilities* under them. In addition to training, effective compliance requires *commitment* and leadership at the top levels of the institution, competent *compliance personnel* with well-defined roles and responsibilities, clearly written *policies and procedures*, sufficient *reporting* and *review mechanisms*, strong *enforcement mechanisms*, and *adequate resources* devoted to the program. Understand

that identifying *institutional obstacles* to compliance and finding ways to overcome those obstacles is an *ongoing task*.

4. Be aware that the protection of *human research subjects* is an area in which all branches of the Government take a vigorous approach to enforcement. Moreover, the relationship between the protection of human research subjects and *financial conflicts of interest* should not be overlooked, although regulatory guidance is still in flux. Recent actions by the OHRP suggest that it is looking to research institutions to enhance their own compliance activities, such an approach will not excuse significant acts of noncompliance with the current regulations. Consequently, ongoing review of applicable regulations and *diligence* on the part of *IRBs* are prerequisites to a successful compliance program.

5. Recognize that the Government has established an extensive set of regulatory and administrative requirements that govern the care and use of *laboratory animals*. The U.S. Department of Agriculture's Animal and Plant Health Inspection Service enforces the Animal Welfare Act through routine *inspections* and, where necessary, substantial *fines*, especially for repeat violations or serious neglect of animal care.

6. Understand the difference between *stem cells* derived from *human embryos* and those derived from *fetal tissue* (so-called germ cells). For human embryonic stem cells, the NIH has established a *registry* of stem cell lines that may be used in federally funded research. Remember that "private" research on unauthorized stem cell lines should be undertaken only after taking steps to ensure that *no federal funds* are used, directly or indirectly.

7. Be aware that *biosafety* is currently a developing area, and that consequently it is important for institutions whose laboratories handle *etiologic agents* to monitor carefully legislation and regulations that may affect their activities. Until new rules have been interpreted, a conservative compliance approach may be warranted. Recognize also that biosafety may fit within your institution's established environmental compliance program, thereby reducing the need to develop an entirely new infrastructure.

8. Bear in mind that there is an increased focus by both the Government and the research community on *financial conflicts of interest*. Emerging issues include *institutional* conflicts of interest and the *HHS "draft interim guidance."* Given the current regulatory climate, your institution may want to review its policies and procedures and consider whether to go *beyond* current regulations. Particular attention should also be given to conflicts of interest that may affect research involving *human subjects*.

9. Watch for agency implementation of the Government-wide "*Federal Policy on Research Misconduct*" through new rulemaking. In the meantime, the ORI model policies and procedures are excellent operational guides.

10. Understand that the *HIPAA privacy regulations* are extremely detailed and complex. Academic medical centers will need identify knowledgeable individuals on whom to rely for guidance to ensure that research is conducted in accordance with the HIPAA privacy regulations.

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