

**Summary of Conference on Research Compliance Challenges
and Opportunities,
May 6-7, 2001**

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the Johns Hopkins University School of Medicine**

Note: This summary reflects some of the workshops and sessions included in the conference. Due to technical difficulties, not all sessions were recorded. For a complete listing of the workshops and sessions, see the conference agenda on the ORI web site. This summary includes the following sessions: 1) Compliance and Institutional Structure, a plenary session; 2) Workshop on Teaching Responsible Conduct of Research; 3) Workshop on Protecting Human Subjects; and 4) Toward an Integrated Approach to Research Compliance, a plenary session.

COMPLIANCE AND INSTITUTIONAL STRUCTURE (PLENARY SESSION)

Dr. Mark Brenner of Indiana University opened the plenary session by describing a 'roles and responsibilities' document developed at Indiana so that policies could be drafted to reflect the roles and responsibilities of various officials involved in research compliance. In addition, Indiana established a web-based approval system to facilitate efficient approvals through the departmental and administrative hierarchies. With respect to research policies, Dr. Brenner recommended that institutions take an inventory of their policies and make them accessible on the web. Ensuring implementation of policies requires a complete educational program. At Indiana, as at many other institutions, many recent educational programs have focused on human subjects research. Indiana's web-based program will be expanded to include all areas of research. Dr. Brenner recommended that educational programs be tailored for their audiences. For example, the content of programs for graduate students may differ from that for principal investigators; programs for biomedical scientists should not be identical to those for behavioral scientists. Course development can be done cooperatively by several institutions.

In addition to delineating roles and responsibilities and educating community members in the responsible conduct of research, it is important to have effective oversight mechanisms. Dr. Brenner recommended user-friendly, Web-based oversight reports to track cost-transfers and other important budgetary issues.

Dr. Brenner described a University-wide compliance committee at Indiana, composed of senior officials responsible for human subjects research, animal research, environmental and radiation issues, internal audits, financial issues, and legal administration. This cooperative approach to research compliance issues is helpful in breaking down barriers between functional units. The committee's objectives are to: 1) ensure that there are "properly functioning programs of internal procedures, controls, communications;" 2) advise the University on compliance and related operational risk; and 3) maximize best practices in research administration. With the assistance of a corporate compliance specialist, Indiana conducted a risk assessment exercise and identified nine areas needing attention. They were: 1) assigning appropriate personnel to each functional unit; 2) ensuring flexibility to respond to new regulations; 3) having adequate oversight; 4) competency and experience among staff; 5) inspections, assessments, and internal and external audits; 6) preparedness for regulatory agency inspection; 7) adequacy of information technology systems; 8) financial operation; and 9) balancing time pressure with the need to observe ethical codes and standards. Determinations were made as to whether each set of issues was high, medium, or low risk.

In summary, Dr. Brenner emphasized the benefit of having a means to assess the status of the areas responsible for research compliance. It allows institutions to report to senior administration and to address

problems common to different areas of the institution, with the ultimate goal of developing and implementing a strong compliance program.

Dr. David Korn of the Association of American Medical Colleges (AAMC) told the audience that he planned to share his observations and reflections based on his experience as a medical school dean and as an association executive. He noted the enormous increase in Federal funding and the increased involvement of industry in biomedical research. These trends have led to a diminution of the public trust in biomedical research and rising concerns about increasingly close relationships between academia and industry.

Dr. Korn cited a 1998 report by the Office of the Inspector General (OIG) of DHHS which highlighted the weakness of the IRB system as a major symptom of the dramatic increase in funding for biomedical research. According to the report, IRBs are understaffed and inadequately trained; they are subject to various conflicts of interest; and it is not clear that they are effective in protecting human subjects. Since the release of the OIG report, OPRR (and its successor agency, OHRP) increased scrutiny of human subjects research programs, temporarily shutting down several prestigious institutions. FDA also increased its compliance activity. A comprehensive review of the IRB system is underway, and Congress has conducted hearings on the protection of human subjects in research. This demonstrates that, in Dr. Korn's view, the academic community has fallen short in its responsibility to protect human research subjects. Dr. Korn noted that anecdotes fueled intense interest on the part of Congress and the public. An August 2000 meeting on conflict of interest and human subject protection drew 700 people, demonstrating the level of concern surrounding the issues. Subsequently, ORI issued a list of several areas in which institutions should be required to provide educational programs for investigators and staff.

Dr. Korn proceeded to describe what the AAMC is doing in response to these issues. He said the Association is focusing on three important areas: 1) advocacy; 2) human subject protection and accreditation of IRBs; and 3) conflict of interest.

In the area of advocacy, AAMC ran several meetings and workshops, which included frank dialogs with NIH and FDA staff. The Association also initiated joint efforts with PRIMR and AAU.

In the area of IRB accreditation, AAMC is working with PRIMR to develop a model for accrediting IRBs. AALAC, the laboratory animal research accrediting body, serves as a model for this effort. Jointly with several scientific and university organizations, AAMC and PRIMR have launched the Association for Accreditation of Human Research Protection Programs (AAHRPP). The members of AAHRPP will function as trustees and will operate separately from the accreditation process. The accreditation program will include a significant proportion of public members, who will represent the interests of patients. Dr. Korn reported that AAHRPP is recruiting an executive director and forming the first accreditation board.

Finally, Dr. Korn addressed the subject of conflict of interest. He noted that conflict of interest in biomedical research was the subject of Public Health Service regulation in the mid-1990's, but that it did not receive substantial public attention until the death of research subject Jesse Gelsinger at the University of Pennsylvania in 1999. Among the first responses to renewed concern about conflict of interest was Harvard Medical School's decision not to relax its relatively stringent policy. Harvard's Dean, Dr. Joseph Martin, assembled a group of deans from the top ten medical schools to systematically address conflict of interest in human subjects research. The group he convened issued a consensus document last winter. Dr. Korn noted that AAMC was taking that consensus document into consideration in its own review of the issue; AAMC recently constituted a task force on conflict of interest. AAMC's task force includes academic leaders, biomedical researchers,

journalists, ethicists, industry representatives, and representatives of patient advocacy organizations. The task force is initially charged with addressing individual conflict of interest in human subject research. It will then turn to the issue of institutional conflicts of interest. Dr. Korn noted that several government agencies, including GAO, NIH, and OHRP, also were addressing conflict of interest policy and management.

In closing, Dr. Korn highlighted the following additional concerns: chronic under- management of research at the university and medical center levels; dramatically increasing commercialization of research, leading to conflicts of interest and blurring of missions; and diminution of public trust in the research enterprise. Rebuilding and maintaining that trust and a consensus in favor of continuing increases in Federal spending on biomedical research are major challenges for the academic research community.

WORKSHOP ON TEACHING RESPONSIBLE CONDUCT OF RESEARCH

Mr. Chris Pascal of ORI noted that the agency's policy on responsible conduct of research was still suspended, but reminded the audience of other ongoing education requirements, including those required by OHRP and NIH. He said ORI planned to meet with scientific societies and to conduct a public meeting to discuss issues related to the policy. Mr. Pascal said ORI was developing a booklet and Web-based responsible conduct of research teaching program that would be available once the policy is implemented. In addition, Federal funds are available to institutions who propose to develop their own courses. The ORI web site contains information on existing resources for the teaching of responsible conduct of research.

Workshop participants also were provided with a history of ORI's involvement in the responsible conduct of research. Promoting responsible conduct of research was described as a logical outgrowth of ORI's traditional area of oversight of research misconduct. Since scientific research has become a collaborative activity and laboratories operate like "small businesses" requiring management skills that most scientists lack, ORI believes its involvement in this field can promote institutional cultures with fewer allegations of misconduct arising from poor management of the research process.

Dr. Frank Macrina introduced the audience to a variety of tools for teaching the responsible conduct of research. He cited curricula developed by UCSD, AAAS, CDC, the University of Minnesota, and Virginia Commonwealth University (VCU). These programs and others cover some or all of the nine areas covered in the pending Office of Research Integrity Guidelines on teaching responsible conduct of research. Dr. Macrina said it is important to communicate principles to students in areas where they have limited experience. Offering small seminars or requiring research papers may enhance electronic or textbook-based teaching. For continuing education of faculty, a teaching format tailored to the needs of full-time investigators is important.

Institutions should evaluate how to most effectively use their time, talent, and money in delivering this instruction. He explained that at VCU, there are three tracks for teaching responsible conduct of research. First, one course is offered twice a year for graduate and postdoctoral students and technicians. Second, faculty must attend two half-day workshops once during the course of three years. The workshops cover all the core instructional areas and employ a case discussion format. Third, administrative, clerical, and fiscal personnel are instructed through a combination of electronic courses and workshops. Dr. Macrina added that, in some VCU departments, undergraduates also are instructed in the responsible conduct of research.

According to Dr. Macrina, some standardization in teaching responsible conduct of research is valuable. However, a single curriculum is not appropriate for every unit in an institution. For example, training in animal care and use may be irrelevant to some researchers and administrators and essential for others.

Mr. Michael Amey discussed the development of the research compliance umbrella at the Johns Hopkins University School of Medicine. In the past, Hopkins simply provided faculty members a copy of the research policies along with their appointment letters. Graduate students were required to attend responsible conduct of research programs. But staff members were assumed to know the elements of their jobs and faculty members were assumed to know how to conduct responsible research. However, serious compliance issues, government audits, and financial penalties levied on institutions around the country highlighted the need for a more systematic approach to compliance education.

A not-for-cause site visit by NIHC--as well as suspensions of human subject research at some major institutions--stimulated discussion of how to improve training and communication with both faculty and staff on compliance issues. The size of the Hopkins constituency and the fact that many investigators and administrators are geographically scattered led to a decision that, initially, in-person training would not be feasible. To address the situation and to enable the institution to track registration for and completion of training, Hopkins decided to adopt a web-based approach to training in the responsible conduct of research. Content was based in part on the University of Minnesota web course in human subjects research; additional content was developed by Hopkins IRB members and staff. (Anticipated additional modules will focus on research with animals; conflict of interest; responsible conduct of research; grants management; and intellectual property.) A custom enrollee database was developed.

Mr. Amey noted that the course is required for all faculty, staff, and students designing or conducting human subjects research, regardless of the source of funding. He indicated that the system is designed to facilitate maximum enrollment in the course, particularly for students outside the U.S. who may not be Hopkins employees.

WORKSHOP ON PROTECTING HUMAN SUBJECTS

Dr. David Cornblath of Johns Hopkins expressed concern that increasing paperwork requirements will lead to avoidance of compliance requirements and may drive talented investigators away from human subjects research. He said he does not believe that a few high-profile cases indicate the system is in crisis. Instead, he said, there needs to be acknowledgment that human subjects research, like any other human endeavor, carries risk and there must be determinations of acceptable risk.

Conducting research to determine the most effective methods for protecting subjects is preferable, according to Dr. Cornblath, to merely increasing paperwork in an apparent effort to protect human subjects. He said research and review of the effectiveness of regulations should be done cooperatively by academia and government. He also called for clarifying the distinctions between guidance and regulation in this field.

Dr. Norman Foster of the University of Wisconsin began his presentation by noting that, prior to the 1970's, before regulations were enforced, there was widespread non-compliance. He also noted that most investigators, IRBs, and regulators act in good faith, but that the parties can and do disagree about the most effective means of accomplishing protection of human subjects.

In Dr. Fost's view, there is "dis-regulation" of human subjects protection. Specifically, the regulations that are in place do not effectively address the protection of subjects, but instead divert money and resources from their actual protection as well as from research. He indicated that in the shutdown of human subjects research at Duke, OHRP acknowledged that there was no risk to human subjects, rather that the University had failed to meet the administrative requirements of the regulations. In fact, the shutdown of research itself had a detrimental impact on subjects.

Dr. Fost detailed several areas in which OHRP's interpretation of the regulations governing IRBs results in the need to fulfill paperwork requirements with no benefit to human subjects. He discussed continuing review, conditional approval, documenting the presence of a quorum, and taking meticulous meeting minutes. Dr. Fost said he estimates the added aggregate cost of meeting the stringent interpretations of the regulations is between half a billion and billion dollars per year nationally. He said each IRB member spends the equivalent of three unpaid forty-hour weeks per year and many members at Wisconsin have quit.

The resources diverted to this "dis-regulation" could, according to Dr. Fost, be directed to activity that would actually benefit human subjects. Examples are improved study design and monitoring of consent forms. Dr. Fost expressed concern that frustration with over-interpretation of regulations and the cost of compliance may lead to decreased compliance with the Common Rule and the shifting of research to other countries. Dr. Fost said he agreed that human subjects research is not in crisis, and the solutions being proffered are not commensurate to whatever problems do exist.

Dr. Ruth Faden of Johns Hopkins noted that her remarks would draw on her experiences as chair of an IRB and as Chair of the Advisory Committee on Human Radiation Experiments. First, she said the Advisory Committee assessed the state of human subject protection in 1994 and concluded that there were major deficiencies in the system. Second, she noted, ethical conduct cannot be regulated. No regulatory system can substitute for trust, integrity, and common values. Dr. Faden also said that scientific research institutions need to be based on cultures that support ethical behavior. She said that systems for protecting human subjects should be designed to focus on the relatively small number of projects that carry the greatest risk. She prefers an emphasis on outcomes to an emphasis on compliance and audits; institutions should develop outcomes measures for human subject protection and assess the outcomes achieved by the regulatory frameworks. Dr. Faden's final observation was that government guidance and regulation is beneficial, but that debate on the issues should continue and government and the research community must remain open to modifying regulations based on the public debate.

The workshop was opened to questions. Asked about affordable internal audit activities, Dr. Fost suggested institutions consider consent monitoring to determine the effectiveness of the consent process. Dr. Sherwin of the University of Pennsylvania noted that his institution developed a system whereby a compliance coordinator from each IRB monitors specific protocols and also ensures consistency across IRBs. His institution tries to devote more resources to high-risk projects than to low-risk projects.

Asked about the acceptability of using commercial IRBs, **Dr. Michael Carome** of OHRP stated that, given the appropriate qualifications, using commercial IRBs was acceptable under the regulations. He said his agency did not have an opinion as to the desirability of using commercial IRBs.

Dr. Fost observed that while commercial IRBs often are well qualified and will assist institutions in complying with regulations, contracting out the work of the IRB can divert resources from an institution's ability to focus on the ethical issues surrounding human subjects research. Developing a local commitment to ethical conduct of

research and discussing difficult issues that arise in behavioral and social science research--such as subjects' privacy--may not be accomplished if the IRB's work is done by an outside group.

Concern was expressed that human subject protection regulation was developed largely to address issues in biomedical research and that the regulations were not suited to social science research. **Dr. Robert Levine** noted that NRPAC, the advisory group to OHRP, was working to address that issue. Dr. Faden stated that research methodologies differ across the social sciences and that regulations should take into account those differences. There was also some discussion about privacy issues and the potential impact of HIPPA regulations on human subjects research.

TOWARD AN INTEGRATED APPROACH TO RESEARCH COMPLIANCE (PLENARY SESSION)

Dr. Chi Dang of Johns Hopkins asked the moderators of each workshop to deliver summaries of the discussions in their respective sessions.

Dr. Richard Traystman of Johns Hopkins, Chair of the Workshop on Animal Care and Use, noted that his panel included representatives from AALAC, OLAW, USDA, and a university. The workshop addressed developing a culture of compliance, establishing performance standards and assessments, and finding resources to support compliance activities. Federal regulations governing animal research, including the proposed regulations for rats, mice, and birds, were discussed. Participants also addressed reducing regulatory burden and paperwork.

The workshop discussed training of IACUC members and investigators, protocol review, and facilities inspection. Inspecting laboratories, particularly in an institution with hundreds of laboratories, was seen as a particular challenge. Other important issues raised were occupational health and safety, animal husbandry, and animal pain and distress. Dr. Traystman observed that AALAC, OLAW, and USDA appear to be working more closely together as a unified regulatory group.

In response to a question concerning veterinary oversight, Dr. Traystman noted that using an outside veterinarian is acceptable if he or she is knowledgeable about the applicable regulations and can effectively assess an institution's level of compliance.

Dr. Robert Levine of Yale University, moderator of the workshop on Protecting Human Subjects, said the panelists brought diverse opinions to the discussion. Dr. Carome of OHRP provided perspective on the agency's high level of activity. According to Dr. Carome, his agency found evidence that at many institutions IRB members and staff were not adequately trained in human subject protection; IRBs tended to have inadequate staff and resources; and many institutions exhibited a lack of commitment to protection of human subjects.

Dr. Joseph Sherwin of the University of Pennsylvania discussed the costs of developing a program of compliance with the regulations administered by OHRP and FDA. He calculated that operating an IRB with a workload of 85 to 100 new cases and 500 continuing reviews per year costs about \$200,000 annually. He noted that the University of Pennsylvania incurred a one-time expense of \$12 million to establish its compliance system and spends at least \$2 million per year to operate the system. Dr. Cornblath of Johns Hopkins said the regulations are not effective in protecting human subjects. He identified several adverse consequences of over-regulation, including diversion of resources from useful administrative activities and from research; increasing reluctance on the part of academic faculty members to serve on IRBs; and potential evasion of the regulations by investigators.

The next speaker in the workshop, **Dr. Norman Fost** of the University of Wisconsin, provided concrete examples of the adverse consequences of over-regulation. He targeted requirements that consume great amounts of time and resources but do not advance the goal of protecting human subjects. **Dr. Ruth Faden** of Johns Hopkins discussed how to achieve an appropriate balance between regulatory compliance and developing a culture that enhances human subject protection. She noted that ethical conduct cannot be created by regulation and added that oversight of protocols should be proportional to the risk each one entails for subjects. She recommended conducting outcomes research on human subject protection measures to determine which are truly effective in protecting subjects.

Dr. Levine closed by stating the need to do cost-benefit analysis of the human subject protection system in order to determine the cost of increased protection at the margins. He added his concern that academic faculty members are discouraged from serving on IRBs.

Mr. Gary Thompson of NIH described the workshop on Fiscal Grants Management. He said that Gil Tran of OMB outlined the rapid growth in grants and contracts during the last ten years. Mr. Tran discussed OMB circulars, cost principles, administrative requirements, and the grant simplification process. The different perspectives of investigators and administrators toward fiscal grants management were addressed by Mr. Thompson. He said it was important to develop a partnership between the faculty member, departmental administrator, and sponsored projects officer. Particularly valuable, he said, is the relationship between the institutional grants administrator and the NIH program administrator. **Mr. Francis Bossle** discussed the institutional perspective and described various initiatives at Johns Hopkins. Among other things, he described a Web-based effort reporting system and early communication with principal investigators when inappropriate spending patterns are identified. It was agreed that an effective system of internal controls helps foster a culture of compliance within an institution.

Dr. Curt Civin, moderator of the workshop on Managing Financial Conflicts of Interest, summarized the remarks of his panelists. In her presentation, Carol Scheman of the University of Pennsylvania set the historical stage for the high level of interest in financial conflict of interest in research. She drew on her experience in developing conflict of interest reporting requirements at the FDA. **Margaret Dale** of Harvard Medical School discussed Harvard's policy and its recent decision to maintain and strengthen, rather than liberalize, a fairly restrictive approach to certain financial interests in research. **Julie Gottlieb** of Johns Hopkins described her institution's policy and procedures for addressing conflict of interest. Dr. Civin reported on that model in some detail. He said the Hopkins approach relies heavily on the input of the Committee on Conflict of Interest, which he chairs. The Committee can recommend that arrangements be prohibited or that they be permitted. When they are permitted, they are allowed to proceed only with several "management measures," including public disclosure of the financial interests; escrow and other restrictions on equity; and oversight of the research potentially affected by the financial interest. Dr. Civin said Hopkins had been using this approach for about a decade. In closing, Dr. Civin called for research to assess the effectiveness of the various approaches being used in addressing financial conflicts of interest in research.

Dr. Sharon Krag of the Johns Hopkins Bloomberg School of Public Health moderated the workshop on Teaching Responsible Conduct of Research. Dr. Krag described the evolution in this field from a focus on recipients of training grants to an ongoing effort to educate all research participants, including faculty, students, fellows, and so on. Dr. Krag said that Mr. Chris Pascal and **Dr. Lawrence Rhoades** of ORI described the areas targeted by ORI's proposed responsible conduct of research training requirements. She noted that the workshop participants identified several other important areas: worker health and safety; environmental health; laboratory safety; grants management; and whistleblower protection. She said Mr. Amey described the web-based training

initiative at Johns Hopkins and Dr. Macrina discussed the variety of CD-Roms, videos, and texts available to teach the responsible conduct of research.