Investigator, IRB and Institutional Financial Conflicts of Interest in Human-Subjects Research: Past, Present and Future

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I. INTRODUCTION

Recent significant injuries, and even deaths of research subjects, have led to a searching examination of how and why these adverse events occurred, how they might have been prevented, whether the human subjects had been fully informed of the risks of the protocols in which they were enrolled, and how financial interests of investigators and institutions hosting the research might have improperly influenced the oversight and conduct of these clinical trials. The most widely known example of this is the death of Jesse Gelsinger in a gene therapy study at the University of Pennsylvania—a study in which, it was later suggested, both the principal investigator and the host institution had pronounced financial interests in the biotechnology agent tested. These financial conflict-of-interest matters lie at the core of ethical issues surrounding clinical trials, and anecdotal evidence suggests that these conflicts are widespread.

The for-profit industry has certainly invested heavily in academia. In 2000 alone, this industry invested approximately fifty-five to sixty billion in research and development, over twice as much spent by the federal government. Seventy percent of that funding reportedly was for clinical drug trials in the United States.

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Investigators may have financial investments in the drug, medical device, or biotech companies whose products they are testing in human trials, and they may receive stipends, speaking fees, consulting fees, or other gifts from these companies. Similarly, academic medical centers, spurred by the possibility of income from technology licensing under the Bayh-Dole Act, also may have such investments, or may receive grants or other income from these companies.

Between 1991 and 1997, university licensing revenues increased from $186 million to $725 million. Moreover, both investigators and institutions hosting research receive some income in relation to most clinical trials, in that compensation for services rendered in these trials supports salaries, institutional overhead, and institutional expenditures for the research itself. Faculty members of academic medical centers, and sometimes the centers themselves, also are increasingly incorporating their own for-profit “start-up” companies to test and develop products originally conceived through basic research conducted at the institution. These faculty members and institutions are typically principal stockholders of the “start-up” company, and faculty members usually serve on the board of directors, as executive officers or as paid consultants of the company. For example, in the Gelsinger case, both the investigator who generated and patented the gene therapy technology and the University of Pennsylvania were shareholders of the “start-up” corporation, Genovo, founded by the investigator to develop that technology. Some academic medical centers have dedicated special space and resources to researchers collaborating with “start-up” companies.

To complicate matters further, industry has, in recent years, been moving away from academia and toward for-profit contract research organizations (“CROs”) and site-management organizations (“SMOs”) that reportedly complete trials more rapidly and more inexpensively than academic medical centers. While approximately seventy-five percent of industry funding for clinical trials went to academia in the early 1990s, this number diminished to less than fifty

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7 Gelsins & Their, supra note 5, at 72.
8 Karine Morin et al., Managing Conflicts of Interest in the Conduct of Clinical Trials, 287 JAMA 78 (2002).
percent by 1995. Like industry itself, CROs and SMOs are culturally
distinct from academia; they are beholden to their shareholders and
less encumbered by academic ideals. Their primary mission is to
conduct trials that will receive approval by the United States Food
and Drug Administration ("FDA"), rather than to advance human
understanding.

This shift in paradigm is generating new issues that will gain
increasing attention over time. For example, with an expanding
number of clinical trials performed by CROs and SMOs, how can we
best assure data integrity and human-subject safety, given the cultural
distinctions between these for-profit entities and academia? Because
CROs and SMOs do not have the same built-in academic values that
were designed to safeguard the missions and purposes of academia,
will greater external protections be required with CROs and SMOs?
The opposite is true today, in that although CROs and SMOs are
subject to FDA regulations governing human-subject research and
financial conflicts-of-interest, neither they, nor their investigators or
senior administrators are governed by other federal conflict-of-
interest regulations because the latter do not apply to privately
funded research.

Another newly-emerging issue is that many academic medical
centers are in the process of transforming themselves to be able to
compete more effectively with CROs and SMOs for industry
funding. These transformations may lead them to operate less like
truth-seekers and more like their for-profit competitors. Depending
on how these transformations unfold, new methods for preserving
academic standards may be needed. With respect to financial
conflicts-of-interest, the questions in need of resolution will continue
to be: 1) whether in particular trials any of these interests exist; 2) the
extent of the interests; 3) and what steps to take in particular trials
when and if such interests rise to a level of significance so as to
influence judgments related to the safety of human subjects and the
collection and interpretation of data.

As noted above and set forth more fully below, there are federal
standards relating to the disclosure and management of financial
conflicts-of-interest. These standards cover, however, only research
studies funded by the United States Public Health Service ("PHS"),
which includes the National Institutes of Health (NIH), the National
Science Foundation ("NSF"), and research that is submitted to

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9 Richard A. Rettig, The Industrialization of Clinical Research, 19 HEALTH AFF. 129
(2000).

10 Bodenheimer, supra note 3, at 1539.
support an industry application to the FDA. Thus, federal standards do not cover many trials. Criticism of the existing regulatory regime has centered not only on the lack of enforced standards for all human-subjects research, but also on the laxity of the existing minimum standards.\textsuperscript{11} There has emerged within American academic medicine and professional associations one school of thought essentially holding that all human-subjects research should be subject to strict financial conflict-of-interest rules, and that those rules should preclude researchers from holding any significant financial interests related to the drugs, devices, or agents they test in clinical trials. The proponents of this position include Dr. Marcia Angell, who has stated that physicians should self-defer from all such investments, and should limit their financial interests to "rubies, racehorses, and real estate."\textsuperscript{12} Similarly, the American Society of Gene Therapy, in the direct aftermath of the Gelsinger case, resolved that their own members should avoid investments or other financial interests in the biotechnology products they investigate.\textsuperscript{13}

On the other hand, many investigators react indignantly to the idea that their integrity should be questioned with regard to their financial interests.\textsuperscript{14} They point out—and, in this assertion, are correct—that there has been no direct proof that financial interests directly and improperly influenced investigators' judgments in the Gelsinger case or in other publicized cases involving possible financial conflicts-of-interest. They also point out that a prohibition on investigators' financial investments related to their research would remove powerful incentives for physicians to undertake research and assist in product development, which in turn would hinder advances in medical knowledge and technology. Medical innovation, particularly in the area of biotechnology, has certainly benefited greatly from close collaboration between industry and academia.\textsuperscript{15}


Indeed, in our experience in counseling academic medical centers, community hospitals, institutional review boards, and investigators, these issues tend to be joined most forcefully in the area of medical devices and biotechnology—sectors of the health care industry in which small and/or “start-up” companies occupy prominent places in product development and manufacture.

In fact, academia-industry partnerships have been credited with the very rise of the biotechnology industry. In pharmaceuticals, however, the primary industrial entities, for many historical, regulatory, and liability reasons, tend to be large, multinational companies that fund the testing of products developed not by physician investigators, but by their own sophisticated in-house research staffs. In such circumstances, physician investigators could have significant investments in a large company’s public securities, but are much less likely to have stock options or intellectual property rights in the drugs they are testing in clinical trials. In addition, even large personal investments in the securities of a multinational pharmaceutical company would tend to be quite attenuated from the results of any one clinical trial, thus lessening a true financial conflicts-of-interest even when an investigator holds, for example, several thousand shares of the company’s stock. The scale of these companies is simply so large that it most often dwarfs any individual’s investment.

An issue closely related to investigator conflicts-of-interest is the possibility of financial conflicts stemming from a hospital or university’s own investments or intellectual property in a product being tested at that hospital or by that university’s faculty. As we noted above, for example, universities may derive considerable revenues from technology transfer agreements. Because the vast majority of licensing income is usually concentrated in only a few inventions, the financial conflicts-of-interest associated with these inventions can be significant, and have led universities to take aggressive action in staking their claim to these profitable inventions. Thus, it has been suggested that institutional financial interests could distort or otherwise improperly influence the exercise

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of judgment by institutional officials with regard to clinical trials, including the Institutional Review Board (IRB) members and research administrators. Unlike investigator conflicts-of-interest, for which there are at least some federal standards, no such standards apply to institutional conflicts. The most that can be said for the application of current federal regulations to institutional conflicts is that they bar IRB members themselves from considering or voting on any protocol in which they have any interest whatsoever, including but not limited to financial interests.

One of the few federal enforcement actions regarding this standard occurred in 2001, when the federal Office for Human Research Protections ("OHRP") found that Johns Hopkins allowed an IRB with a conflicting interest to consider and discuss, but not vote on, a proposed study.19 Yet such enforcement actions are rare, and one wonders how IRBs across the nation actually implement this apparent "zero tolerance" standard for IRB members. If indeed not a scintilla of possible conflicting interest in an IRB member were to be tolerated, one could posit that an IRB member who is a responsible and/or senior institutional official should recuse himself or herself from considering and voting upon a trial in which the institution itself has some financial interest in the outcome. It is only at this point, in fact, that current federal regulations can be thought to touch at all on the institutional conflicts issue.

The research world is, for all these reasons, in the midst of a heated debate about what should be appropriate processes and standards relating to investigator and institutional financial conflicts-of-interest. Among the recent sentinel events in this debate have been: 1) the issuance in late 2000 by OHRP of a Draft Interim Guidance on these issues,20 the commentary on this draft guidance provided by the National Human Research Protections Advisory Committee ("NHRPAC"),21 which is an advisory committee to the

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19 See Letter from OHRP, to the Johns Hopkins University School of Medicine (July 19, 2001) (regarding Human Subjects Protections Under Multiple Project Assurance (MPA) M-1011).
21 Letter from NHRPAC, to the Honorable Tommy G. Thompson, Secretary of
Secretary of the United States Department of Health and Human Services (the "Department"); 2) the issuance of guidance in late 2001 by the Association of American Universities ("AAU");22 3) and the issuance of two separate reports by the Association of American Medical Colleges ("AAMC"), one on investigator conflicts-of-interest and the other on institutional conflicts-of-interest.23 The outcome of the debate will hopefully be an approach toward investigator, IRB, institutional, and other financial conflicts-of-interest that sustains the motivational, collaborative, economic, and productivity benefits of academic-industry relationships. Such relationships have led to so many staggering medical innovations and advancements, while assuring that the primary missions and values of academia are not compromised along the way. The purposes of this article are to analyze the current federal regulations; identify their gaps in coverage; describe the approaches recommended by NHRPAC, AAMC, and AAU; to fill these gaps; and suggest some other possible approaches to these issues.

II. CURRENT MINIMUM FEDERAL REGULATIONS RESPECTING FINANCIAL CONFLICTS-OF-INTEREST IN HUMAN-SUBJECTS RESEARCH24

As set forth above, there are three sets of federal regulations now in effect that address the issue of financial conflicts-of-interest held by clinical investigators, including their immediate family and, to a large extent, their research staff. Those are the regulations of the Public Health Service (PHS), the National Science Foundation (NSF),


the FDA. The major features of these regulations are set forth below. With regard to the critical gaps in coverage, one should note that these regulations only cover human-subject research that is either funded by PHS or NSF, or that is used for an application to the FDA. Thus, a large section of research is excluded, including investigator-initiated research and industry or foundation-sponsored research not used for an FDA application. Further, even within the federal regulations, there are limiting thresholds on the definition of financial interests covered, with those thresholds varying between the PHS/NSF regulations and the FDA standards. Moreover, there is no regulation whatsoever governing the amount of compensation that flows from research sponsor to investigator and/or host institution as payment for services related to a clinical trial itself.

Although such compensation can be substantial—so substantial as arguably to influence research results—that compensation avoids review and regulation as the laws are now written. Finally, and perhaps most importantly, all of the existing federal regulations were written with one goal in mind: research integrity. The other primary goal of most research regulations—the protection of human subjects—is nowhere to be found in the text or spirit of these existing regulations, as is readily apparent from the lack of any requirement for disclosure of significant financial interests to IRBs or to prospective research subjects. These are among the most critical gaps in current regulations to be identified in the current debate, but must be understood in the context of that which these regulations currently do require.

A. Public Health Service Regulations

"Investigations" covered by PHS regulations include "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."25 This definition also extends to the spouse and dependent children of the Investigator.26 No specific category or status of researcher is automatically extended or included within the definition, unless that researcher is not involved in research funded by PHS. Rather, the institution accepting PHS funds must determine which individuals, regardless of their seniority or their inclusion or exclusion in the grant proposals, meet the functional definition set forth in these regulations.27

26 Id.
27 Id.
Initially, a “Significant Financial Interest” is broadly defined to encompass anything of monetary value, including cash, consulting fees or honoraria, stocks or other ownership interests, patents, copyright or other intellectual property rights, and the royalties from the intellectual property rights. The regulation then proceeds to exclude various types of financial interests from the reporting requirement. Salary and other compensation from the institution conducting the research are not incorporated in the definition of “Significant Financial Interest.” Similarly, “Significant Financial Interest” excludes income from seminars, teaching, or lectures sponsored by, as well as income from serving on advisory committees or review panels for public or not-for-profit entities. Further, this regulation does not cover relevant financial interests if: (i) all payments in one year to the Investigator, including payments to his or her spouse and dependent children, are not expected to be more than $10,000; or (ii) if the relevant ownership interest of the Investigator, and spouse and children, is worth less than $10,000 and does not constitute more than a five percent ownership interest in a single organization. Further, not all “Significant Financial Interests” must be disclosed to the institution accepting grant money, as explained below.

An institution must require each investigator who will participate in PHS-funded research to submit, for review by an official at the institution, a listing of that investigator’s known Significant Financial Interests and those of his or her spouse and dependent children: “(i) that would reasonably appear to be affected by the research for which PHS funding is sought; and (ii) in entities whose financial interests would reasonably appear to be affected by the research.” The regulations do not provide any guidance as to how an Investigator should determine whether the “Significant Financial Interest” “reasonably appears” to “affect” the research. Therefore, under the PHS regulations, if a “Significant Financial Interest” is present but does not “reasonably appear” to affect the research, then the “Significant Financial Interest” need not be reported. The Investigator must make the financial disclosures to the institution by the time a grant application is submitted to PHS, and then updated

28 Id.
29 Id.
30 Id.
32 Id.
either annually or as new reportable “Significant Financial Interests” are obtained.\textsuperscript{34} An institution must take reasonable steps to ensure that if it carries out any research through contractors, subgrantees, or collaborators, then any Investigators working for those contractors or collaborators must also comply with the institution’s disclosure policies. An example of a reasonable precaution might be a process whereby a designated institutional administrator is responsible for verifying whether or not contractors, subgrantees, or collaborators are involved in a research project, and is responsible for obtaining the written assent of any such individuals to the institution’s research policies.

The information that Investigators must disclose to the institution is more detailed than that which the institution must report to the government, and the institution has some discretion in determining which of the Significant Financial Interests that are disclosed to the institution must be reported to the government. Specifically, an institution must certify in its applications to PHS that before spending any PHS grant money, the institution will report to PHS “the existence of a conflicting interest (but not the nature of the interest or other details)” and assure PHS that it will manage, reduce or eliminate the “conflicting interest” in accordance with the regulations. The institution has sixty days to report any conflicting interests that it identifies after submitting the initial report. Under the regulations, a reportable “conflict-of-interest exists when the designated official(s) reasonably determines that a Significant Financial Interest could directly and significantly affect the design, conduct, or reporting of PHS-funded research.”\textsuperscript{35} The institution must certify that it will make available to the Health and Human Services (HHS), upon request, information regarding all conflicts-of-interests which the institution has identified and how it has dealt with those interests to protect the research from bias. Thus, the category of “Significant Financial Interests” reportable to the government is narrower than the category of “Significant Financial Interests” that researchers must report to their institutions.

An institution is required to establish guidelines for the designated official to identify conflicting interests and take action to ensure that the “conflicting interests will be managed, reduced or eliminated.”\textsuperscript{36} The institution must maintain a system to enforce these policies regarding conflicting financial interests and to sanction

\textsuperscript{34} Id.
\textsuperscript{35} 42 C.F.R. § 50.605(a) (2002).
\textsuperscript{36} 42 C.F.R. § 50.604(d).
violators as appropriate. The regulations list some of the potential methods and conditions that may be utilized by an institution to manage the conflicts-of-interest. Pursuant to these enumerated methods, an institution could:

1. publicly disclose the financial interest;
2. have independent reviewers monitor the research;
3. modify the research plan;
4. disqualify certain Investigators from participation in the research;
5. require the Investigator to divest the Significant Financial Relationship; or
6. sever relationships that create actual or potential conflicts.  

In addition, the institutions may develop reasonable alternative solutions for managing the conflicting interests may be developed by the institutions.

If the design, conduct, or reporting of the research has been biased by the failure of an Investigator to comply with the institution's conflict-of-interest policy, then the institution must notify PHS of the corrective action it has taken or will take. Remedies available to the government for violations of these policies include the right of the unit of PHS funding the research to suspend funding until the conflict-of-interest is resolved. Further, if HHS determines that an Investigator had a conflicting interest which was not disclosed or managed in accordance with the PHS regulations, and the purpose of the funded clinical research was the evaluation of safety or effectiveness of drugs, medical devices, or treatment, then the institution must require that the relevant Investigator disclose the conflicting interest in every public presentation of the research results.

B. National Science Foundation Regulations

The NSF conflict-disclosure requirements are similar to those of PHS. The distinctions from the PHS requirements are set forth below. Perhaps the most significant distinction is that although all PHS-funded research is subject to the PHS conflict disclosure requirements, not all institutions accepting NSF grant funds are bound by the NSF conflict-of-interest policies. Rather, the NSF policy is applicable only to institutions with more than fifty employees. Further, the NSF policy is not explicitly applicable to subgrantees, collaborators or consultants. Nevertheless, subgrantees or consultants may be bound by a similar policy at their own institutions.

37 42 C.F.R. § 50.605(a).
NSF expects that an institution accepting NSF grant funds would obtain an assurance from the institution that employs the collaborating investigator indicating that the Investigator has complied with the policy at his or her own institution.

The definition of “investigators” to whom the NSF policy applies within the institutions bound by NSF conflict-of-interest policies, as well as the nature of the investigators’ Significant Financial Interests that must be disclosed to the institution, are the same as those set forth in the PHS regulations. An exception is that the relevant research and conflicts-of-interest arise out of grants funded by NSF rather than PHS. While the NSF Grant Policy Manual does not set forth many requirements for conflict-of-interest policies, the manual references guidance by university associations and scientific studies, which may assist an institution in developing its own conflict-of-interest policies. Unlike the PHS regulations, the NSF policy does not affirmatively require an institution to advise the investigator of its conflict-of-interest policies; but presumably it would be extremely difficult for an institution to comply effectively with the NSF policies without an advisement to its investigators.

The NSF policy allows an institution more discretion than that allowed by PHS in its obligation to manage the “conflicts-of-interest,” which phrase is defined in the NSF policy in exactly the same manner as the PHS regulations, enabling the institution to make policy decisions on the value of managing the conflict at issue. If the individual designated by the institution to review the investigator financial disclosures determines that

imposing conditions or restrictions [on the Investigator] would be either ineffective or inequitable, and that the potential negative impacts that may arise from a significant financial interest are outweighed by interests of scientific progress, technology transfer, or the public health and welfare, then the [designated institutional] reviewer(s) may allow the research to go forward without imposing such conditions or restrictions.

While the PHS regulations require, as noted above, that the institution report to the federal government the existence of a conflicting interest held by one of its investigators, and assure that the interest has been “managed, reduced or eliminated,” the NSF policy only requires the reporting, to the Office of General Counsel of NSF, of any “conflicts-of-interest” that have not been “satisfactorily” managed, reduced, or eliminated prior to spending any NSF grant funds. Accordingly, the institution need not assure NSF that the
conflicts will be managed or eliminated. The institution is not required to report to NSF conflicts-of-interest that are managed prior to spending funds.

C. Food and Drug Administration Regulations

The FDA reporting requirements apply to a pharmaceutical company or other party that has submitted a marketing application (and is therefore an "applicant") to the FDA for approval of a human drug, device, or biologic product, and has submitted to the FDA the results of "covered clinical studies" as a proposed basis for FDA approval. A "covered clinical study" is defined as "any study of a drug or device in humans submitted in a marketing application . . . that the applicant or the FDA relies on to establish that the product is effective . . . or any study in which a single investigator makes a significant contribution to the demonstration of safety."\(^{58}\) A "clinical investigator" is "a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects."\(^{59}\) As with the definition of "Investigator" used by PHS, this term includes the spouse and dependent children of the clinical investigator.

Although the clinical investigators do not have a direct reporting obligation to the FDA, they are obligated by the regulations to provide the research sponsor with sufficient financial information to enable the party supporting the study at the time it was conducted (the "sponsor") to meet its disclosure obligations to the FDA. The applicant—generally, the pharmaceutical or medical-device company—must submit to the FDA a list of all clinical investigators who conducted covered clinical studies to determine whether the product meets the FDA marketing requirements. The applicant must note which of the investigators are employees of the sponsor.

For every clinical investigator who participates in a covered clinical study, the applicant must disclose to the FDA, using Form FDA 3455, the nature of the following financial interests of the clinical investigators:

(i) any financial arrangement between the sponsor and the clinical investigator, where the value of the compensation to the investigator for conducting the study could be influenced by the outcome of the clinical studies, such as payments which are higher for a favorable study outcome, including royalty payments for sales of

\(^{58}\) 21 C.F.R. § 54.2(e) (2002).

\(^{59}\) 21 C.F.R. § 54.2(d).
the product or an ownership interest in the sponsor of the study; (ii) any other compensation from the sponsor of the study to the investigator or the institution to support activities of the investigator that is worth more than $25,000 (not including the costs of conducting the study), which is given while the clinical investigator is conducting the study, or within one year after completing the study; for example, grants for ongoing research, equipment and honoraria; (iii) any property or financial interest in the tested product held by the clinical investigator, including patents, copyrights or licensing agreements; (iv) any ownership or other financial interest (including stock and stock options) in the sponsor held by the clinical investigator, the value of which cannot be easily determined by reference to public prices, or any ownership interest in a publicly traded company that exceeds $50,000 during the time that the investigator is conducting the study or within one year after completion of such study; and (v) any steps taken to reduce the bias created by these disclosed financial relationships. 40 For any clinical investigator who has no such financial interests, the applicant must submit a Form FDA 3454, certifying the absence of these financial interests.

The FDA evaluates all the disclosed information and considers any safeguards included in the study design that may provide protection against bias created by the disclosed financial interest. If the FDA determines that the financial interests of the clinical investigator raise questions about integrity of the data, the FDA has the right to conduct audits of the data from the questioned clinical investigator, request further analyses, request independent studies, and refuse to consider the data from the covered clinical study. The applicant must maintain a file of certain financial interests of the clinical investigators for at least two years after the date of approval of the FDA application. Upon request by the FDA, the applicant must make these records available for access and copying by the FDA.

Importantly, however, these reports flow directly from investigators to sponsors, thus bypassing institutions, such as academic medical centers and hospitals that host clinical research and institutional IRBs. Moreover, if the research is conducted at physicians’ offices, there is no effective conflict-of-interest oversight at all, except through the IRB that has approved and is overseeing the research. Yet in our experience, IRBs rarely investigate or consider these issues outside an institutional research context. For all these reasons, some host institutions are now requiring both sponsors and

investigators to provide copies of all FDA financial investment disclosure forms to the IRB or a conflict-of-interest committee. In addition, host institutions are cross-checking the information contained on these FDA forms with the information provided by investigators directly to the institution through the institution’s conflict-of-interest processes.

III. DRAFT INTERIM GUIDANCE FROM THE OFFICE OF HUMAN RESEARCH PROTECTIONS AND COMMENTARY ON THAT DRAFT GUIDANCE BY THE NATIONAL HUMAN RESEARCH PROTECTIONS ADVISORY COMMITTEE

In August 2000, the United States Department of Health and Human Services held a public conference at the National Institutes of Health on human-subjects protection and financial conflict-of-interest. The conference’s deliberations made it clear that there has been wide recognition among the national research community of the gaps in regulation and oversight, and in institutional regulation and oversight of financial conflicts-of-interest. In the aftermath of the meeting, the Department issued a document for public comment, Draft Interim Guidance: Financial Relationships in Clinical Research: Issues for Institutions, Clinical Investigators and IRBs To Consider When Dealing with Issues of Financial Interests and Human-Subject Protection (the “Draft” or “Draft Interim Guidance”), in order to recapitulate the issues and positions that prevailed at the August 2000 conference. In that Draft, the Department: (i) suggested that institutions develop financial disclosure processes for all IRB members and all researchers involved in human-subjects research; (ii) endorsed the creation of conflict-of-interest committees to consider financial interests disclosed and to recommend conflicts management strategies, with its work coordinated with that of the IRB; (iii) indicated that IRB members should be chosen with a view to minimizing institutional conflicts-of-interest; and (iv) suggested that institutions take affirmative measures to manage institutional conflicts. The Draft also asserted that IRBs need to consider disclosure of financial conflicts as a primary method of protecting human subjects and assuring full informed consent. One of the most revolutionary aspects of that document, however, was the simple recognition that institutional conflicts are very important to research integrity and human-subjects protection, even

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41 Part III is adapted from the NHRPAC Letter, supra note 20, which was primarily authored by Mark Barnes, but which also included comments and suggestions from all members of NHRPAC and from Greg Koski, M.D., Ph.D., former Director, OHRP.
though specific measures to control those conflicts were not suggested. The draft was published in January 2001 for public comments.

The challenge of commenting on the Draft Interim Guidance was taken up by the Department’s own research advisory committee, NHRPAC. NHRPAC has, as part of its charter, the responsibility and duty of advising the Department and the Director of OHRP on significant issues in the regulation and oversight of human-subjects research. NHRPAC’s particular duty is to advise on issues relating directly to the welfare and safety afforded those persons who agree to participate in human-subjects research. During the summer of 2001 as part of that mission, NHRPAC undertook, through a convened Working Group and discussions and deliberations at its plenary meetings, to examine the current status of Department regulation and oversight of conflicts-of-interest that can occur in human-subjects research, focusing primarily on financial conflicts-of-interest. These conflicts-of-interest considered by NHRPAC related to investigators, other research staff, IRB members, and institutions or entities that conduct research or monitor the research process. Although the Department’s Draft Interim Guidance had been general in its tone and content, and vague in many of its recommendations, the NHRPAC commentary was much lengthier and more specific, and within the national research community, quickly gained the status of prevailing wisdom on conflict-of-interest issues.

According to NHRPAC and to the Department’s Draft Interim Guidance, the implied threat of a financial conflict-of-interest held by any party participating in research is that such a conflict could provide incentives for that party to compromise communications to patients, or decisions, judgments, or reports at any point (or multiple points) in the research process, in order to serve that financial interest, when and if the financial interest conflicts with the values of truth and integrity. NHRPAC noted that although data to substantiate a correlation of remuneration with inappropriate professional judgment are limited, a meta-analysis of twenty-nine studies published in the Journal of the American Medical Association in January 2000 indicated that financial remuneration and benefits flowing from vendors significantly influenced physician-prescription patterns, even though one would expect that physician prescriptions to patients should be impelled only by the patient’s best interests. To NHRPAC, the corollary in human-subjects research was that the

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promise of money or stock interest could distort investigators’ and other parties’ judgments, actions, and communications to patients.48

Many of the comments received by the Department on the Draft Interim Guidance disputed the need for the issuance of the guidance, contested the form of the guidance itself, and asserted that any additional Departmental guidelines or regulations should await the outcome of processes by which AAMC, AAU and other associations were seeking to craft their own “best practices” guidelines. In the aftermath of the Gelsinger case, NHRPAC understood the insufficiency of data on these issues, yet recognized the compelling need to assure the welfare of research subjects and research integrity. The majority of NHRPAC, therefore, endorsed the Department’s efforts to provide careful, limited guidance, with provision made for periodic review and revamping of guidelines. NHRPAC asked, however, that HHS not portray or regard the guidance as a regulatory requirement, but instead as a template for continued dialogue with professional and trade organizations and the research community. In NHRPAC’s view, with multiple financial interests held by researchers and institutions increasingly common, and multiple adverse research events involving questionable investigator and/or institutional judgment reported to also involve questionable financial relationships, the Department’s guidance was sorely needed. NHRPAC opined that Department inaction in these circumstances could undermine public confidence in the overall enterprise of human-subjects research.

A. Defining “Conflict-of-Interest”

NHRPAC encouraged the Department to be careful in distinguishing between a duty to disclose or a process of disclosure of financial interests, on the one hand, and identification of a financial interest as a conflict-of-interest, on the other. In many cases in the Draft and in the course of the NIH meeting on conflicts-of-interest in August 2000, the term “conflict-of-interest” had been used, for example, to signify the presence of any financial interest. This seemed to NHRPAC to be an inappropriate, inexact and overly broad use of the term, because the mere presence of a financial investment or relationship does not necessarily result in a meaningful or

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48 For a recent review of the evidence supporting a correlation between financial interests and professional decision-making in both clinical practice and in research-related activities, see Mark Barnes & Patrik S. Florencio, Financial Conflicts of Interest in Human Subjects Research: The Problem of Institutional Conflicts, 30 J.L. MED. & ETHICS 390, 391 (2002).
significant conflict-of-interest that must be managed. At the same time, although the approach of the Draft Interim Guidance seemed to emphasize a "financial-relationships" approach, it had not fully captured the core of the moral and legal concerns; namely, that some financial relationships in research may be so significant as to present a true conflict of moral and legal duties among researchers and institutions. The term "financial relationship" was therefore thought not entirely accurate in describing the issue that has recently caused much consternation in the research community and among the regulatory authorities, especially because some financial relationships are so trivial or so attenuated that they cannot be thought of as posing any significant risk of a "conflict-of-interest." In making this distinction, NHRPAC placed itself firmly on the side of those who, although concerned with disclosure and management of conflicts-of-interest, also saw that some level of significance was needed, with defined thresholds for interests to be reported and managed.

On this issue, NHRPAC recommended that disclosure policies include some threshold amount below which a financial interest (e.g., investments, stock holdings, honoraria, paid travel expenses) is so minute or attenuated that it cannot be said to constitute a conflict-of-interest, or even a "complicating financial relationship." Indeed, as described above, existing PHS, NSF and FDA regulations allow de minimis exceptions to their disclosure requirements, just as certain fraud and abuse statutes and regulations also allow such exceptions to general prohibitions. NHRPAC noted in its deliberations that increasingly, institutions that conduct research have adopted the PHS standard of a $10,000 interest or five-percent ownership in an enterprise that would "reasonably appear to be affected by the research"44 as applied across-the-board to all research, regardless of the source of funding. Those institutions therefore have calibrated their disclosure and conflict-management processes to these thresholds. In the absence of consistent federal regulations on this point, and with FDA and PHS standards in conflict, NHRPAC endorsed the lower PHS threshold as appropriate for institutional policies, and suggested that the Department also adopt the PHS standards as applying to all research. Moreover, NHRPAC recommended that the PHS standards be applied to all research, regardless of source of funding, recognizing that the risk of degradation of research integrity and subjects' informed consent cannot be regarded as limited by source of research funding.

Significantly, NHRPAC recommended that disclosure and

analysis of conflicts-of-interest in research should include dollars flowing to researchers and institutions from the research itself, and should not be limited solely to other financial arrangements between sponsors, researchers and institutions. For example, "enrollment bonuses" are not uncommonly given as compensation within the research arrangement itself, and those bonuses have aroused considerable concern. In addition, compensation terms for the researcher are dictated by research contracts, and are subject to change during the research, but initial research contracts and amendments to them are not routinely vetted in most institutions by an IRB or a conflict-of-interest committee. Thus, in fact, institutions and their IRBs are often ignorant of the contractual and financial arrangements between researchers and sponsors. To NHRPAC, the standard to be applied to such intra-research arrangements was that in the process of research, investigators and institutions receive compensation only within the broad parameters of "fair market value" of services rendered. The "fair market value" standard is, in fact, used in other areas of health care law, such as qualifying medical service arrangements as not violative of the federal Anti-Kickback Laws.\(^4^5\)

In many areas of medical research, and in our experience counseling clients, particularly in the areas of orthopedics and cardiology, it is quite common for physician investigators to have significant ownership interests in the devices or products they test in clinical trials. In many cases, this occurs because the physicians themselves have invented the devices or products, or have contributed to their development. In such cases, the argument has been made that these physicians are in fact uniquely positioned, due to their unique prior knowledge to test these devices with the greatest safety to human subjects. Heeding these arguments, NHRPAC asserted that conflict-of-interest analysis should take account of, and contain "compelling and necessary" exceptions for, situations in which physicians who treat unusual conditions, invent new devices, or develop other interventions, and yet have significant financial interests in those techniques, interventions, or devices. NHRPAC contended that in these cases, guidance should not discourage these physicians from inventing new devices and developing new interventions and therapies, and should not prohibit these physicians from acting as clinical investigators, particularly in the initial stages of investigation, because they may be in the best position to undertake critical research with a high assurance of safety for research subjects.

\(^4^5\) 42 U.S.C. § 1320a-7b(b) (2002).
NHRPAC recommended the development of methods to assess and monitor conflicts-of-interest in these situations, and to protect patients, without preventing essential clinical research.

B. The Financial Disclosure Process

The financial disclosure process calls for the disclosure of an investigator's and institution's most private and confidential financial information. This is true both of disclosure processes that are annual and complete in form, and those that call for disclosure of interests on a protocol-by-protocol basis. A lack of confidentiality in the disclosure of financial interests therefore would serve as a disincentive for researchers to disclose, especially in "close" cases in which their financial interests' relation to the research is attenuated or unclear (for example, if they own significant financial interests in a company offering a product that competes or would compete with the product under investigation). NHRPAC therefore suggested—just as many conflicts-of-interest processes now stipulate—that financial disclosure policies for IRB members, IRB staff, investigators, and institutions include strict confidentiality protections for the information disclosed in order to protect the privacy interests of those involved in the research enterprise.

The recommended form and methods of financial disclosure were not clearly set forth in the Department's Draft Interim Guidance. Also unclear, but critical, was the relation of financial disclosure and conflict-of-interest process to IRBs and IRB deliberations. NHRPAC tried to clarify this by strongly indicating that an IRB should have ultimate plenary authority to examine potential conflicts-of-interest and to approve or disapprove research, all stemming from the IRB's overarching role in protecting human subjects. Yet there has also been a profound doubt that IRBs have the expertise or staff support that would allow them to undertake insightful analysis of financial interests and conflicts-of-interest.

Further, to the extent that any non-affiliated members of the IRB have no legal obligation to maintain the confidentiality of information derived from the IRB process, an IRB's consideration of financial information could result in inappropriate disclosures of

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45 C.F.R. § 46.109(a) (2002); 21 C.F.R. § 56.109(a) (2002).

even non-conflicting interests.

For these reasons, NHRPAC thought it unwise and inappropriate to place on IRBs the responsibility for collecting financial information and then analyzing that information to identify and suggest remedies for conflicts-of-interest. Instead, NHRPAC recommended the adoption of a research-related, conflict-of-interest process that would operate within the institution's existing conflict-of-interest and compliance mechanisms. In most institutions (including, for example, federal employment), there are existing conflict-of-interest processes that do not in any way depend on IRBs and that are, in fact, much broader in their scope than research activities. For example, they cover purchasing, outside employment, outside activities, and investments and family interests in potential vendors of goods and services. To accomplish these purposes, most hospitals of moderate or large size have designated personnel, in human resources departments or elsewhere within the entity, who bear the responsibility of collecting this information from employees and professional staff at periodic intervals, and then analyzing that information and taking appropriate actions.

In regard to the relation of IRBs to a conflict-of-interest process, NHRPAC recommended that conflict-of-interest disclosure and analysis be regarded as a necessary adjunct of the regular IRB approval process. Just as IRBs may have adjunct bodies reporting to or assisting them, such as biosafety committees, radiation committees, finance office staff (to advise on costs to patients enrolled in research), and/or "privacy boards" (as outlined in the HIPAA regulations), so too an IRB could (and according to NHRPAC, should) appropriately avail itself of a conflict-of-interest committee or one or more administrators charged with performing the necessary duties of collecting and analyzing information related to financial disclosures. Under the system that NHRPAC recommended, the

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48 See, e.g., 45 C.F.R. § 164.512(h)(i)(B) (2003). Another related example would be a Data Safety Monitoring Board ("DSMB"). DSMBs are sponsor-assigned committees that monitor the investigators' performance, assess the safety of human subjects, and judge whether experimental treatments are effective. See Janet Wittes, Behind Closed Doors: The Data Monitoring Board in Randomized Clinical Trials, 12 Stat. Med. 419, 420 (1993). DSMBs are commonly used in multi-center clinical trials, and are composed of experts who have no personal connection to the trials, but whose expertise extends to the clinical conditions and/or experimental agents or methodologies being studied. DSMBs are created and used by research sponsors, but their reports, distilling and interpreting multiple significant adverse events reports, are often provided to IRBs either by the sponsors or by investigators, and allow the IRBs meaningful access to expert advice on the meaning of adverse events reports.
conflict-of-interest committee would digest this information for the IRB, and make a formal report to the IRB regarding conflicts-of-interest, if any, identified in its review of financial disclosures related to the research application. The conflict-of-interest committee would also make recommendations to the IRB as to methods that appropriately manage conflicts. In this scheme, the report from the conflict-of-interest committee would serve as a necessary part of the research application.

The IRB, holding ultimate legal authority over approval of research, could accept, modify, or reject the conflict-of-interest committee's suggestions in this regard, based on its own deliberations and any submissions from the researchers or institution. If, on the other hand, a conflict-of-interest committee made specific recommendations relating to conflicts management or concluded that the research project was so potentially corrupted by financial interests that it should not go forward, presumably an IRB could ignore such recommendation(s), but should do so only under compelling and highly unusual circumstances. In fact, it would be nearly unthinkable (if only as a matter of risk management) that an IRB would ignore a conflict-of-interest committee's recommendation on these issues, or that a health care facility's administration would allow research to proceed if its IRB had significantly relaxed the recommendations of a conflict-of-interest committee. According to the Common Rule, while institutions may not approve research that has been turned down by their IRB, institutions may forbid the initiation or continuation of any research study having received IRB approval, or may require investigators to comply with greater safeguards than those imposed by the IRB. To ensure that host institutions are granted the opportunity to review cases where their IRB disagrees with any finding by the conflict-of-interest committee that a financial interest constitutes a conflict-of-interest, or where their IRB weakens the committee's suggested management strategies, we have recommended to our clients that the matter should automatically be referred to a designated senior official at the institution for review and resolution.

Although the Department's Draft Interim Guidance clearly addressed conflict-of-interest issues in the context of academic medical centers and hospitals, an increasing amount of human-subjects research is occurring in the setting of private physicians' offices, outside the purview and control of institutional IRBs or

49 45 C.F.R. § 46.109(a) (2002); 21 C.F.R. § 56.109(a).
50 45 C.F.R. § 46.112.
conflict-of-interest processes. CROs and SMOs, for example, employ community physicians to recruit patients for participation in clinical trials. For independently-conducted research, such as research funded through private sponsors and occurring in physicians’ offices not tied to hospitals or other institutions (e.g., outpatient clinical trials conducted by independent practitioners), NHRPAC found a profound need for guidance, and ultimately for some sort of regulation, on conflicts-of-interest. Although some “freestanding” commercial IRBs include financial conflicts-of-interest as part of their overall review of the research, these commercial IRBs might themselves be considered conflicted given that their services are usually purchased by research sponsors.\footnote{Trudo Lemmens & Benjamin Freedman, \textit{Ethics Review for Sale? Conflict of Interest and Commercial Research Review Boards}, 78 \textit{Milbank Q.} 547 (2000).} Commercial IRBs that too often make recommendations that are adverse to their clients’ interests or wishes may soon find themselves out of business. For independently-conducted research, NHRPAC recommended that mandates are given only to IRBs with sufficient expertise in financial conflicts-of-interest to review and make recommendations regarding such conflicts, or that such IRBs develop affiliations with experienced conflict-of-interest committees or similar processes in place at other entities.

\textit{C. Institutional Conflicts-of-Interest}

As noted, the Gelsinger case at the University of Pennsylvania raised new issues relating to institutional investments and financial interests in products being tested. In fact, an entirely new category of troubling financial relationships in research emerged from Gelsinger and other recent cases of alleged research misconduct, in which hospitals, clinics, and other entities that “host” research themselves possess investments or financial interests in the products being tested, or in the companies that own those products. Among the risks here is that IRB members often include department chairs, deans, mid- and high-level administrators from the entity, and researchers. Any of these people may understand the value of these investments to the institution, and their judgments on research approval and oversight could be altered by countervailing concerns for patent value, stock price, or related financial interests. This countervailing interest may be as attenuated as the desire to protect the overall fiscal health of the entity, or as narrow and parochial as seeking to guarantee personal end-of-year bonuses by preventing erosion of the value of intellectual property related to ongoing research studies. The reality
of the risk of institutional conflicts, however, lies in the subtle and not always immediately detectable influence that the prospect of institutional "windfalls" may have on an IRB primarily composed of persons from that institution. Awareness that their research could affect their own institution's financial health may influence the researchers who are amassing and analyzing data, if their institution holds a significant stake in the drug or device being tested.

In late 2001 and in 2002, the financial services industry noted concerns relating to institutional conflicts-of-interest and their effects on employees. These concerns have arisen from incidents in which employees of financial services firms allegedly gave inaccurate investment advice to investors, and that advice encouraged investments in business entities in which the employee and his employer (usually a financial services firm) maintain a substantial financial interest. In other words, concerns have emerged about the extent to which investments and financial relationships of the research analyst and his employer compromise the integrity of professional-investment advice. These concerns have resulted in a significant revision in disclosure obligations imposed upon research analysts and their firms by their trade organization, the National Association of Securities Dealers ("NASD") and by the Securities and Exchange Commission ("SEC").\footnote{National Association of Securities Dealers, NASD Rule 2711, Research Analysts and Research Reports, available at http://www.nasd.com/pdf-text/rf02_21_final.pdf; Securities and Exchange Commission, Amendments to NYSE Rules 472 and 351, available at http://www.nyse.com/pdfs/2002-49fil.pdf (last visited Oct. 31, 2002).} The recommended solutions to these "institutional" conflicts include, in the proposed SEC regulations: (i) disclosure of financial and institutional interests in publications and media appearances; (ii) prohibitions on personal investment transactions inconsistent with rendered or published financial advice; and (iii) "coding-off" periods in which underwriting of a securities offering by a financial services firm must preclude that firm's research analysts from opining about the offering for a defined post-offering period. Other proposed reforms would prevent executives in the merchant banking and securities underwriting sectors of a financial services firm from supervising analysts or setting analyst compensation. In this way, in substantive areas outside of clinical research, institutional conflicts--and the pressures that such conflicts may place on the institution's employees--have recently been determined to merit significant regulatory attention. Most significantly, the proposed regulatory response focuses on disclosure of interests, and the control of conflicts by "walling off" personnel
from one another within the same entity.

Consistent with these developments in the financial services sector, NHRPAC suggested that conflict-of-interest-committee recommendations to the IRB on how to manage institutional interests that rise to the level of a troubling financial relationship or an actual conflict-of-interest might include: (i) requiring independent monitoring of informed consent and patient enrollment; (ii) independent expert evaluation of data interpretation and analysis; or (iii) separation of research staff by function and role within an approved protocol. We recently recommended that policies on institutional financial conflicts of interest be drafted to require the divestiture of research-related economic interests by “institutional decision makers” (including trustees, presidents, chancellors, provosts, deans, department chairpersons), IRB members, and any other persons at institutions who are responsible for overseeing the safety of clinical trials.58 This recommendation is a logical extension of the policy underlying the law which already prohibits IRB members from possessing financial interests in the research they review.

D. Disclosure of Financial Conflicts to Human Subjects

One of the most difficult issues in establishing a conflicts-of-interest process is the extent to which troubling financial relationships or possible conflicts, once identified, must be disclosed to research subjects, or potential subjects, in the informed consent process. This was, in fact, the issue that in some ways most offended the families in the Gelsinger and Fred Hutchman Cancer Center cases. These families charged that they had not been informed of the researchers’ and institutions’ financial investments, and that had they been so informed, their family members would not have consented to enrollment in the trials. Unfortunately, the scholarly literature on disclosure of physician and institutional remuneration to patients deals primarily with disclosure to patients of incentives for treatment under managed-care contracts, and its findings are inconclusive. Further, under existing legal and ethical standards, not all risks must be disclosed in the informed consent process, but only “material” risks; the corollary would be that if a troubling financial relationship or conflict-of-interest exists, it should be disclosed only if the risk that flows from it cannot be eliminated or managed, and thus reduced

below the level of a "material" risk to research subjects. NHRPAC's general sense was that research subjects should be informed of "real" problems relating to relevant financial relationships and conflicts-of-interest, but should not be burdened with information about arcane and speculative problems. At the same time, however, due to a pressing need to bolster public confidence in the research enterprise, the majority of NHRPAC felt that information regarding a troubling financial relationship or possible conflict-of-interest, once identified in the conflict-of-interest process, should be, in principle, available to, or affirmatively disclosed to, research subjects.

How to tell patients in a meaningful and understandable way about these relevant financial relationships and conflicts, and about potential risks flowing from them, is a largely undefined process with no clear precedents. A very real risk here is that if presented with confusing, chaotic, and detailed but undigested information about investments, compensation, and money flows, patients could be utterly confused, and their ability to make reasoned choices impaired rather than assisted. Another very real risk is that patients may defer from participating in research if troubling financial relationships are exaggerated, or ways of managing them are unclear. Efforts to inform patients about their own medical care often appear in long documents that patients sign but do not read, suggesting that both in medical care and in clinical research, physicians and other providers need to find ways to communicate risks and their management more clearly, accurately, and effectively. For these reasons, NHRPAC suggested that conflict-of-interest committees must be careful to identify when a possible conflict exists, and when it does not (in which case, no disclosure would be necessary).

Faced with a pressing need to provide some practical advice to IRBs, NHRPAC advised that in a research protocol in which an actual conflict-of-interest was identified in the financial disclosure process, subjects could be advised in the informed consent process (and/or in the form itself) of the possible conflict and the nature of that conflict, with the terms, conditions and extent of disclosure calibrated by the conflict-of-interest committee and the IRB to correspond to the level of risk that the possible conflict poses. According to NHRPAC's commentary, conflict-management strategies should also be disclosed, so that research subjects have general knowledge of the conflict-of-interest identification and management processes, and how those apply to the study in which the subjects are considering enrolling. Conflicts management strategies cited by NHRPAC included mandating independent monitoring of informed consent, outside evaluation of subjects' eligibility for a trial, independent
review of adverse events reports and research records, and peer review of data analysis and interpretation. NHRPAC referred to this method of disclosure of specific financial interests and specific conflicts management strategies as "specific" disclosure of possible conflict-of-interest.

Alternatively, in cases in which the possible conflict is less tangible and more speculative, the IRB and the conflict-of-interest committee could choose, according to NHRPAC, to advise the potential research subjects in a more generic way during the disclosure process of the potential conflicts in the study. The subjects would be advised of the fact that steps have been taken to manage the possible conflicts, the availability of additional information on these conflicts, and the safeguards that have been utilized to manage them from the researcher or the research coordinator. In this scenario, however, this initial disclosure would not contain specific mention of where the possible conflict resides or of actual financial interests held. This method of disclosure was referred to by NHRPAC as "generic" disclosure.

NHRPAC even provided a suggested form of disclosure:
Every research scientist and physician at Mercy Hospital, and Mercy Hospital itself, must disclose significant financial interests in private companies or entities that may be related to this research study. Our Hospital committees have reviewed this information and have concluded that there are some financial relationships between the researchers or Mercy itself on the one hand, and the company that is funding this research, on the other. [insert some degree of specific disclosure here, if warranted, as to the interests and the conflicts management strategies]. However, after considering this information, our Hospital committees believe that there are no conflicts-of-interest that [or no conflicts-of-interests that, when taken with the conflicts management strategies discussed above] will influence the way you will be treated in this study or the way in which this research study will be conducted. If you would like to have more information about Mercy Hospital's review process in general, or in regard to this study, please ask the researchers or the research coordinator, and they will assist you. You may also ask Mercy Hospital's patient advocate, who also can arrange for you to have this information. If, because of this information, you choose not to participate in this study, this will have no effect in your continued health care at Mercy. Participation in all research, including this study, is entirely voluntary, and you may withdraw
from participating at any time.\textsuperscript{54}

Such information in the informed consent form could in fact serve to inform potential research subjects of the process and the existence of significant and relevant financial interests. In addition, as NHRPAC proposed, subjects who are concerned about these issues would be invited, if interested, to seek more detailed information. In this model, the IRB, the conflict-of-interest committee, researchers, and administrators would be under an obligation to respond accurately to subjects who ask for additional information regarding an institution’s or IRB’s disclosure and conflict management procedures (with thresholds), or information regarding the actual financial interests involved in the study and the ways in which those possible conflicts are being managed.

The issue of the extent and form of disclosure to prospective research subjects was hotly contested during NHRPAC’s deliberations, and required several revisions to its final commentary on the Department’s Draft Interim Guidance. A minority on NHRPAC preferred that all actual relevant financial relationships (whether for the investigator or the institution) be disclosed in writing as part of the informed consent process, in order to provide complete transparency to research subjects. A majority, however, declined that approach, citing several reasons. First, such an approach, they argued, could result in informed consent forms becoming even more complicated than they are already, which the majority regarded as promoting confusion among subjects rather than comprehension. Second, under the scheme proposed by NHRPAC, institutions and researchers would be required actively to disclose and evaluate financial relationships in all research activities, regardless of source of funding, and to manage all possible conflicts or troubling financial relationships identified. In fact, research should not, in NHRPAC’s proposed and preferred approach, be allowed to proceed unless the actual risks from troubling financial relationships have already been reduced to a level below “significant” through conflicts management strategies. Therefore, under NHRPAC’s recommended approach to these issues, disclosure of troubling financial relationships or actual conflicts to research subjects would not be the preferred methodology for protecting subjects. Rather, it would be an adjunct method for allowing subjects to have access to information that some may find relevant to their choices to participate in research. Finally, the NHRPAC majority felt that an unvarying requirement that researchers’ personal and private

\textsuperscript{54} See NHRPAC Letter, supra note 21, at 12.
financial information be published in widely circulated and easily available informed consent forms would not be respectful of researchers' own privacy interests, and should be employed only where the IRB and the conflict-of-interest committee required such disclosure. The risk of abuse of such personal information could act ultimately as a disincentive for some physicians and others to act as investigators. At the same time, there was consensus among the NHRPAC members that researchers (and institutions) must recognize that when they have direct personal financial investments in a research item or device, research subjects' safety and independent decision-making must take priority over researchers' and institutions' financial privacy.

In summary, on the issues of disclosure to research subjects, a majority of NHRPAC preferred the approach of financial disclosure, conflicts analysis, conflicts management, and carefully calibrated “specific” disclosure, or “generic” disclosure, with more specific information readily available to patients upon their request. Under those recommendations, therefore, institutional and researcher disclosure and recommendations regarding management of conflicts would be transmitted to the IRB and would precede research approval; the IRB would make its determinations on the management of conflicts and the scope and nature of disclosures to research subjects; and simple disclosure to research subjects would not, in any event, be substituted for the duty of an IRB, institution, or researcher aggressively to identify and manage possible conflicts according to their established processes.

IV. REPORTS BY THE ASSOCIATION OF AMERICAN UNIVERSITIES AND THE ASSOCIATION OF AMERICAN MEDICAL COLLEGES

In the wake of NHRPAC’s commentary, the AAU and AAMC both addressed the issue of financial conflicts-of-interest on behalf of their members, and both issued reports regarding their findings and conclusions. The reports were released in close succession; the AAU report was issued in October 2001 and the AAMC report in December 2001. Both reports are largely consistent with, and therefore lend support to, NHRPAC’s commentary on the Department’s Draft Interim Guidance and NHRPAC’s general findings and recommendations regarding financial conflicts-of-interest in human-subjects research. The AAMC report begins by noting in the introduction, as it did in its 1990 report on conflicts-of-

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55 See AAMC Report 1, supra note 23; see also AAU Report, supra note 22.
interest in research,\textsuperscript{56} that there is nothing intrinsically inappropriate about investigators receiving financial rewards from their research endeavors, and by acknowledging that the integrity of many investigators' research will not be affected by their financial interests in that research. Nevertheless, significant financial holdings in the subject matter of the research, or in the sponsor of that research, can create the appearance of bias, and, according to the AAMC, institutions should be as concerned with the appearance of bias as they are with actual bias.\textsuperscript{57} The emphasis on maintaining an appearance of neutrality and integrity is grounded in the oft-quoted argument that public trust in the research enterprise is eroded when investigators (and/or institutions) appear biased.\textsuperscript{58} Similarly, the Ethics Manual of the American College of Physicians has underscored that the mere appearance of impropriety can undermine trust in the medical profession.\textsuperscript{59} Moreover, as noted by the AAU in its report, if institutions do not adequately self-regulate themselves to the satisfaction of the public and government regulators, government agencies may perceive the need to adopt more prescriptive approaches to the oversight of financial conflicts-of-interest through, for example, formal guidance documents or regulations.\textsuperscript{60} The risk to institutions is that the formal measures adopted by such government agencies may be unnecessarily onerous and more costly to implement than would be self-imposed regulatory mechanisms for managing financial conflicts-of-interest. Thus, it is

\textsuperscript{56} Association of American Medical Colleges, \textsc{Guidelines for Dealing With Faculty Conflicts of Commitment and Conflicts of Interest in Research} (1990), available at http://www.aamc.org/research/dbr/coi.htm (last visited May 1, 2003).

\textsuperscript{57} See AAMC REPORT I, supra note 23, at 4.

\textsuperscript{58} See id. ("[i]mportantly, however, though a researcher may strive to insulate his or her decision-making from bias, the mere appearance of a conflict between financial interests and professional responsibility may weaken public confidence in the researcher's objectivity. The real and apparent risks posed by financial interests likewise have the potential to threaten public support for the research mission of academic institutions. The credibility of academic medicine and the public trust we prize so highly could be undermined by revelations that an institution has failed to exercise rigorous oversight of financial interests in human subjects research and may therefore have exposed those subjects to avoidable harm."); see also Arnold S. Relman, \textit{Economic Incentives in Clinical Investigation}, 320 NEW ENG. J. MED. 933 (1989); Jerome P. Kassirer, \textit{Medicine at Center Stage}, 328 NEW ENG. J. MED. 1268 (1993); Catherine D. DeAngelis, \textit{Conflict of Interest and the Public Trust}, 284 JAMA 2237 (2000); Donna Shalala, \textit{Protecting Research Subjects -- What Must Be Done}, 343 NEW ENG. J. MED. 808 (2000).


\textsuperscript{60} See AAU REPORT, supra note 21, at 15; see also Jerome P. Kassirer, \textit{Pseudoaccountability}, 134 ANN. INTERN MED. 587 (2001).
risky, and unquestionably insufficient, for investigators and institutions to claim that the research being conducted at the institution is protected by virtue of being subject to the highest scientific standards. Not surprisingly, both the AAMC and the AAU recommended that institutions proactively develop policies and procedures for eliminating and reducing real and apparent financial conflicts-of-interest. Moreover, as NHRPAC had suggested, both the AAMC and the AAU recommended that institutional policies on financial conflicts-of-interest apply uniformly to all research conducted at the institution, regardless of whether that research is publicly or privately funded.\textsuperscript{61}

According to the AAMC, the bedrock principle of institutional policies should be a rebuttable presumption against allowing investigators with one or more significant research-related financial interests from conducting such research at the institution.\textsuperscript{62} Also consistent with NHRPAC commentary, the AAMC guidelines adopted the PHS definition of "significant financial interest," namely, an expected return of more than $10,000 to the researcher and/or to the researcher's spouse and dependent children when all financial holdings in the research have been aggregated over one year, or, if the relevant ownership interest of the researcher and/or spouse and dependent children is worth more than $10,000, a more than five-percent ownership interest in a single organization.

As discussed above, PHS regulations require investigators to report their relevant significant financial interests to the host institution. Under the AAMC guidelines, these reportable significant financial interests would then subject the investigator to a rebuttable presumption against allowing the research to proceed. Financial interests below the PHS threshold are considered to be \textit{de minimis} under both the PHS regulations and the AAMC guidelines. Investigators with \textit{de minimis} financial interests are not required to report the nature and extent of their relevant financial interests to the host institution because these interests are considered to give rise to only weak conflicts-of-interest that are unlikely to jeopardize research integrity or human-subject safety and welfare. These investigators must nevertheless file a report with the host institution affirming that they do not have any significant financial interests that would reasonably appear to be affected by their current or anticipated research activities. The AAU went one step further than

\textsuperscript{61} See AAMC REPORT I, \textit{supra} note 23, at 7; see also AAU REPORT, \textit{supra} note 22, at 5.

\textsuperscript{62} See AAMC REPORT I, \textit{supra} note 23, at 7.
the AAMC, NHRPAC and existing PHS regulations by recommending that institutional policies require the disclosure of all relevant financial interests that could give rise to conflicts-of-interest.\(^{63}\) This is also the approach that we, on occasion, have counseled our clients to take because it avoids the problem of leaving to investigators the sometimes complicated task of deciding whether their interests lie above or below the reporting threshold, especially in the case of intangible yet expected future earnings, such as stock options or royalty income.

Under the AAMC standard, research by investigators with significant research-related financial interests, or with any research-related financial interests under the AAU standard, is generally prohibited absent “compelling circumstances” to justify the performance of the research by the conflicted investigator. The “compelling circumstances” exception to the prohibition on the performance of research by conflicted investigators is not significantly different from NHRPAC’s “compelling and necessary” exception, described above. Although the AAU did not explicitly define the term “compelling circumstances,” the AAMC considered such circumstances to exist where the investigator is “uniquely qualified by virtue of expertise and experience” to conduct the investigation.\(^{64}\) In our own judgment, compelling circumstances may also exist when the host institution or facility where the proposed research is to be conducted has special facilities or equipment that are unavailable at most other institutions and would allow or facilitate the proposed research, or when the investigator or the host institution is particularly well situated to enroll study subjects because of the patient population or catchment area of the institution. Applying these criteria, where compelling circumstances exist and the benefits derived from these circumstances are determined to outweigh the risks posed by any conflicts-of-interest, the presumption would be rebutted and the research could proceed at the institution subject to appropriate oversight. Where compelling circumstances do not exist, the presumption would, of course, not be rebutted and the research would be prohibited from proceeding at the institution for as long as the investigator maintained any relevant significant financial interest(s) (in the case of the AAMC guidelines and according to NHRPAC's proposed approach), or for as long as the investigator maintained any research-related financial interest(s) (in the case of the AAU guidelines).

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\(^{63}\) See AAU Report, supra note 22, at 4, 9.

\(^{64}\) See AAMC Report I, supra note 23, at 7.
Like NHRPAC, both the AAMC and the AAU recommended that disclosure of significant financial interests be made to an institutionally designated conflict-of-interest committee, rather than to the institution's IRB.\(^6\) This approach is consistent with PHS regulations that vest authority for reviewing significant financial interests, and for suggesting management strategies on how to eliminate or reduce such conflicts, in "institutional official(s),"\(^6\) rather than explicitly in the IRB. This may have been done out of concern for the fact that IRBs are already overburdened and do not necessarily have the technical expertise to evaluate and recommend corrective actions to remedy financial conflicts-of-interests. Nevertheless, because IRBs retain overall supervisory responsibility for human-subjects research conducted at institutions,\(^7\) NHRPAC, the AAMC, and the AAU have all recommended that conflict-of-interest committees inform IRBs of their determination regarding whether any conflicts-of-interest exist, and if so, of their recommended management strategies regarding those conflicts.\(^8\) Unlike NHRPAC, however, which recommended that IRBs to be given plenary authority to modify the findings or recommendations of the conflict-of-interest committee, including the authority to weaken or even outright reject those findings or recommendations, both the AAMC and the AAU have recommended that in the case of disagreement between the IRB and the conflict-of-interest committee, the more stringent of the findings or proposed management strategies be decisive.\(^9\) NHRPACs recommended approach emphasizes the Common Rule requirement that IRBs be given the authority to approve or disapprove all research conducted at federally funded institutions, whereas the AAMC and AAU approach attempts to reconcile that Common Rule requirement with the fact that PHS regulations vest institutional officials (i.e., the conflict-of-interest

\(^{6}\) See AAMC REPORT I, \textit{supra} note 23, at 14; \textit{see also} AAU REPORT, \textit{supra} note 22, at 7.

\(^{6}\) 42 C.F.R. § 50.604(b), (d) (2002).


\(^{8}\) See AAMC REPORT I, \textit{supra} note 23, at 14; \textit{see also} AAU REPORT, \textit{supra} note 23, at 5.

\(^{9}\) See AAMC REPORT I, \textit{supra} note 23, at 8 ("[t]he Task Force recommends that as between the conflict of interest committee and the IRB, the more stringent determination should be dispositive."); \textit{see also} AAU REPORT, \textit{supra} note 21, at 6 ("Universities should consider designing systems so that an IRB also may determine if there is a financial conflict of interest that needs to be managed, or if a management plan implemented by the conflict of interest committee or official should be made more stringent. In such a system, neither the IRB nor the conflict of interest committee would be able to override the other’s management requirements if the result would be to lessen the stringency of the management requirements.").
committee) with decision making authority over financial conflicts-of-interest. Reconciliation is achieved by equally distributing final decision-making authority over financial conflicts-of-interest between the IRB and the conflict-of-interest committee, because the more stringent findings and recommendations prevail with neither institutional body having a veto power over the other. Because the law on this matter is unclear, absent further guidance from regulatory agencies, institutions should feel free to adopt either approach.

As we noted above, one of the revolutionary aspects of the Department's Draft Interim Guidance is that in addition to addressing investigator financial conflicts-of-interest, which by that time had been recognized as an issue in need of guidance by the majority of the research and bioethics communities, the Draft Interim Guidance also recognized that institutional financial conflicts-of-interest are as deserving of consideration as investigator conflicts. Unlike investigator financial conflicts-of-interest, for which there exists some formal oversight through the PHS, NSF, and FDA regulations discussed above, no laws or regulations currently govern the conflicts-of-interest of institutions and/or their senior directors and trustees. In its commentary on the Department's Draft Interim Guidance the NHRPAC addressed and itemized the issue of institutional financial conflicts-of-interest, NHRPAC's commentary provided one of the first thorough, albeit preliminary, analyses of this newly evolving topic. The AAU has also provided its members with some preliminary guidance on institutional conflicts-of-interest. A few core principles regarding institutional conflicts that can be derived from the AAU's Report are: (i) institutional conflicts can arise from corporate (i.e., the institution or a subdivision of the institution) or individual (i.e., senior management, trustees, department chairs) relationships with, or financial holdings in, industry; (ii) there is no de minimis threshold below which the conflict should be considered insignificant (i.e., all relationships or financial interests are viewed as potential conflicts); (iii) the appearance of bias is as important as actual bias; and (iv) if conflicts are not managed they can lead to improper decision making. The AAMC recently published a report on institutional financial conflicts-of-interest.70 Some of the central tenets of that report are: (i) the affirmation of the AAU finding that institutional conflicts can emanate from the financial holdings of an institution as well as from the financial holdings of an institutional official; (ii) that institutional conflicts are best managed through the separation of responsibility

70 AAMC REPORT II, supra note 23.
for oversight of human-subjects research from responsibility for institutional investment activities and technology transfer programs; and (iii) that in certain predefined circumstances (e.g., where an institution has an equitable interest of any value in a non-publicly traded sponsor of human-subjects research at the institution, or an equitable interest worth more than $100,000 in a publicly-traded sponsor at the institution), institutional conflicts ought to be vetted by an institutional entity charged with oversight and management responsibility for such conflicts. Although the thoughtful commentaries on institutional financial conflicts-of-interest provided by NHRPAC, the AAU and the AAMC were a much needed and welcomed commencement toward defining and devising coping strategies for managing conflicts-of-interest that arise and operate at the institutional level, further analysis on this issue is needed.

Like the AAMC, we have recommended that the primary methods for controlling institutional financial conflicts-of-interest should focus on assuring adequate separation of research activities from institutional investment activities, and instituting independent monitoring for clinical trials. 71 The institutional body or entity responsible for independent monitoring should have expertise in financial investments, the handling of intellectual property, and the process of human-subjects research. That institutional body or entity should also be sufficiently autonomous from the investigators, the IRB, the conflict-of-interest committee, and the institution generally. We have termed that institutional entity an “independent review committee” (“IRC” or “independent review panel”) in order to emphasize that a primary characteristic of the entity must be the necessary independence to conduct an impartial and reliable review of whether the institution’s financial holdings and relationships constitute actual conflicts-of-interest, and if so, to recommend adequate safeguards for assuring that those conflicts do not affect research integrity or subject safety. While no member of the IRC should have responsibility for the institution’s financial well being, nor should any member be associated with any research that could benefit directly from the financial investments or relationships under review, the IRC should be composed of persons having at least some affinity for, and/or loyalty to, the institution so that IRC recommendations are consistent with the institution’s long-term interests while assuring subject safety and research integrity.

The overarching goal of the IRC should be to isolate and neutralize the potential ill effects of the conflicts-of-interest, rather

71 See Barnes & Florencio, supra note 42 at 399.
than outright elimination of all financial relationships whenever possible. Although management stratagems for dealing with institutional financial conflicts-of-interest are now increasingly proposed, more in-depth examination of how institutional conflicts-of-interest can affect research (including the collection of empirical data on this matter if possible), and how such conflicts can be most efficiently and effectively mitigated, is greatly needed. However, because our goal should be to maximize the benefits of industry-academia collaboration while minimizing the risks associated with such partnerships, including the risks associated with financial conflicts-of-interest, future work in this area should attempt to incorporate risk-benefit analyses of different types and levels of oversight into their recommendations. Further scholarship is particularly needed to address the issue of CRO and SMO financial conflicts-of-interest, and the issues surrounding the slow transformation of those academic medical centers that are positioning themselves to regain the market share of industry clinical trial funding they have lost in recent years to CROs and SMOs. Such analysis is also needed to address investigator financial conflicts-of-interest that occur in regard to physician office-based clinical trials, where no institutional conflict-of-interest committee is available.

CONCLUSION

The research enterprise is one of humankind's most exciting undertakings, and in many respects one of its noblest. Medicine can be said to derive nobility from its care and treatment of the sick and the dying and scientific research from its quest to advance human understanding. These raisons d'être are, in the abstract, good and pure. As in all other areas of human activity, these beneficent pursuits can at times conflict with the personal interests of those privileged with the responsibility for carrying out these professional missions. Thus, physicians and researchers will, at some point during their careers, inevitably encounter circumstances in which their personal interests are at odds with the noble and self-sacrificing characteristics of their profession. In both professional undertakings, financial conflicts-of-interest are among the most likely conflicts to be encountered. In the research world, the close partnerships that have developed between academia and industry over the past three decades have led to a significant increase in the amount of financial conflicts-of-interest that most investigators will be required to face during their professional careers, thereby intensifying the need to multiply the number and/or the potency of the countercincentives favoring the finer attributes of scientific research, including research
integrity and special care for the human subjects who agree to participate in clinical trials. These close partnerships have also created new and expanding financial conflict-of-interest issues, such as the issue of institutional financial conflicts-of-interest which stem in part from the Bayh-Dole Act of the early 1980s. The solution to dealing with these financial conflicts-of-interest is not to dismantle the partnerships that have yielded so many medical innovations that have been used to advance health and alleviate human suffering, but to devise and implement the necessary safeguards to ensure that the human-subjects research enterprise is held to the highest standards of science and ethics. While the implementation of these substantive and procedural safeguards might require additional procedures, considerations and controls—rarely favored by physicians and researchers understandably eager to advance medical science—this option is better than building impenetrable walls around academia or risking the ethical integrity of human-subjects research itself.