interest could be directly and substantially affected by the research, and the degree of risk to the human subjects involved that is inherent in the research protocol. The committee should also consider the extent to which the interest is amenable to effective oversight and management.

Conducting Research means, with respect to a research protocol, designing research, directing research or serving as the principal investigator, enrolling research subjects (including obtaining subjects' informed consent) or making decisions related to eligibility to participate in research, analyzing or reporting research data, or submitting manuscripts concerning the research for publication.

Covered Individual includes any faculty (fully-, partially-, or non-salaried) or faculty agent, staff, student, fellow, trainee, or administrator who, under the aegis of the institution or pursuant to the review and approval of the institution's IRB, conducts research involving human subjects.

Disclosure means a release of relevant information about significant financial interests in human subjects research to parties outside the institution's COI review and management processes (e.g., to research subjects or journal editors).

Financially Interested Company means a commercial entity with financial interests that would reasonably appear to be affected by the conduct or outcome of the research.[13] This term includes companies that compete with the sponsor of the research or the manufacturer of the investigational product, if the covered individual actually knows that the financial interests of such a company would reasonably appear to be affected by the research. This term also includes any entity acting as the agent of a financially interested company (e.g., a contract research organization).

Financially Interested Individual means a covered individual who holds a significant financial interest that would reasonably appear to be affected by the individual's human subjects research.

[13] Under the standard articulated in the PHS regulations, institutions must solicit and review information about investigators' significant financial interests in any entity "whose financial interests would reasonably appear to be affected by the [PHS-funded] research." 42 C.F.R. §50.604(c)(1)(ii).

Human Subjects Research includes *all* research meeting the definition of "research" performed with "human subjects" as these terms are defined in the federal Common Rule (45 C.F.R. Part 46 and 21 C.F.R. Part 56), regardless of the source of research funding or whether the research is otherwise subject to federal regulation. In the event that the Common Rule definitions of "human subjects" or "research" are modified through rulemaking, any such revisions shall apply for the purposes of this guidance.

Rebuttable Presumption Against Financial Interests in Human Subjects Research means the institution will presume, in order to assure that all potentially problematic circumstances are reviewed, that a financially interested individual may not conduct the human subjects research in question. This rule is not intended to be absolute: a financially interested individual may rebut the presumption by demonstrating facts that, in the opinion of the COI committee, constitute compelling circumstances. The individual would then be allowed to conduct the research under conditions specified by the COI committee and approved by the responsible IRB.

Reporting means the provision of information about significant financial interests in human subjects research by a covered individual to responsible institutional officials and to the institutional COI committee, or the transmission of such information within institutional channels (e.g., from the COI committee to the IRB).

Responsible Institutional Official means a Dean, Provost, CEO, or other institutional official who is responsible for the oversight of research programs within the institution.

Responsible IRB is the institutional review board (or boards) with jurisdiction over the research as specified in the multiple projects assurance (MPA) (or the federal-wide assurance (FWA)) that the institution has provided to the U.S. Department of Health and Human Services, or as otherwise established under DHHS or FDA regulation or policy.

Significant Financial Interests in Research include the following interests of the covered individual (and his or her spouse and dependent children), or of any foundation or entity controlled or directed by the individual or his or her spouse:

- Consulting fees, honoraria (including honoraria from a third party, if the original source is a financially interested company), gifts or other emoluments, or "in kind" compensation from a financially interested company (or entitlement to the same), whether for consulting, lecturing, travel, service on an advisory board, or for any other purpose not directly related to the reasonable costs of conducting the research (as specified in the research agreement), that in the aggregate have in the prior calendar year exceeded the de minimis amount established in PHS regulation (presently $10,000), or are expected to exceed that amount in the next twelve months.
- Equity interests, including stock options, of any amount in a non-publicly-traded financially interested company (or entitlement to the same).
- Equity interests (or entitlement to the same) in a publicly-traded financially interested company that exceed the defined de minimis amount (see exceptions below).
- Royalty income or the right to receive future royalties under a patent license or copyright, where the research is directly related to the licensed technology or work.[14]
- Any non-royalty payments or entitlements to payments in connection with the research that are not directly related to the reasonable costs of the research (as specified in the research agreement between the sponsor and the institution). This includes any bonus or milestone payments to the investigators in excess of reasonable costs incurred, whether such payments are received from a financially interested company or from the institution (note *prohibition* in B(11) on milestone payments tied to the achievement of particular research results).
- Service as an officer, director, or in any other fiduciary role for a financially interested company, whether or not remuneration is received for such service.

Exceptions. Significant financial interests in research *do not include* the following:

- Interests of any amount in publicly traded, diversified mutual funds.
- Stock in a publicly-traded company that (when valued in reference to current public prices) meets the de minimis criteria established in PHS financial dis-

[14] When evaluating future royalty interests, in addition to the factors listed in the definition of compelling circumstances, the COI committee might consider the anticipated time interval between the research and marketing approval of the investigational product.

closure regulations (presently, an interest that does not exceed $10,000 in value and does not represent more than a 5% ownership interest in any single entity).

- Stock options in a publicly-traded company that (when valued using accepted valuation methods) meet the de minimis criteria established in PHS financial disclosure regulations (presently, an interest that does not exceed $10,000 in value and does not represent more than a 5% ownership interest in any single entity).
- Payments to the institution, or via the institution to the individual, that are directly related to reasonable costs incurred in the conduct of research as specified in the research agreement(s) between the sponsor and the institution.
- Salary and other payments for services from the institution.

B. Scope and Substance of Policy

1. **Conflict of Interest (COI) Official and Committee.** Federal regulations require PHS-funded institutions to appoint a COI official to review financial interests in PHS-sponsored research.[15] The Task Force recommends that institutions also establish a standing COI committee.[16] COI committee membership should include individuals who conduct human subjects research at the institution, as well as the institution's COI official and other officials experienced in the oversight of conflicts of interest and familiar with applicable laws and regulations. A liaison to the IRB is recommended. Institutions might also consider means of involving community or patient representatives in the COI oversight process.

   Institutions should ensure that the COI committee responsibilities include the following:

   a. Review of any request by a financially interested individual to rebut the presumption that he or she may not conduct human subjects research.

   b. Documentation of the committee's findings and the bases for any recommendation to permit or to recommend against permitting a financially interested

[15] 42 C.F.R. § 50.604(b).

[16] References in this guidance to the "institution's COI committee" apply to the institution's COI official in the event that an institution chooses not to establish a standing COI committee.

individual to conduct human subjects research. In either case the COI committee should prepare a summary report describing the nature and amount of the financial interest and the committee's recommendations. This summary report should be made available to the IRB. When the COI committee has recommended that a financially interested individual be permitted to conduct human subjects research and the IRB has approved the research and the individual's participation, the summary report should be provided to research subjects or the public, upon request.

c. *Management and oversight* when a financially interested individual is permitted to conduct human subjects research. As a first principle, the COI committee should encourage the financially interested individual to minimize the potential for conflict of interest by reducing or eliminating the interest or the individual's direct involvement in the research. The COI committee should specify the monitoring procedures or other conditions to be imposed when a financially interested individual will be permitted to conduct human subjects research.

d. *Communication* to the IRB, and to responsible institutional officials, of summary information about the nature and amount of any significant financial interest in human subjects research, along with the committee's findings and recommendations concerning requests by financially interested individuals to conduct such research.

2. **Process.** Every institution should adopt mechanisms that ensure the following:

   a. The financial reports of covered individuals are collected and maintained in a format that is readily accessible to the COI committee and responsible institutional officials;

   b. The responsible IRB and responsible institutional officials are alerted whenever a financially interested individual proposes to conduct human subjects research;

   c. Prior to the IRB's final approval (whether initial or continuing approval) of human subjects research, the COI committee has informed the IRB and responsible institutional officials of any significant financial interests held by

financially interested individuals who will conduct the research, as well as the COI committee's findings and recommendations concerning the same;

d. Financially interested individuals are provided an avenue for appealing decisions of the COI committee; and

e. When financially interested individuals will be permitted to conduct human subjects research, the financial interests in question are disclosed in accordance with the institution's COI policies.

3. **Written Policy.** Every institution engaged in human subjects research should have a written policy on financial interests in such research. This policy should define all key terms clearly and should detail substantive prohibitions and restrictions, as well as the procedures for reporting financial interests, reviewing financial reports, disclosing reported information, implementing the policy, appealing decisions concerning the policy, and sanctioning non-compliance with the policy The written policy should explain the criteria that the COI committee will apply when reviewing a request by a financially interested individual to rebut the presumption that he or she may not conduct human subjects research. The policy and related information should be readily accessible to covered individuals and to the public; in addition to conventional means of communication, the policy should be placed on the institution's website, if one exists.

4. **Rebuttable Presumption that Financially Interested Individuals May Not Conduct Human Subjects Research.** The policy should establish the presumption that, in the absence of compelling circumstances, a financially interested individual may not conduct human subjects research. This presumption should be rebuttable when compelling circumstances exist.

   a. The policy should allow the COI committee, after it reviews the relevant facts and circumstances and documents the compelling circumstances, to recommend that a financially interested individual be permitted to conduct the research, and to make recommendations for appropriate monitoring and oversight.

   b. A summary report indicating the nature and amount of the financial interest and COI committee recommendations should be transmitted to the responsible IRB and to responsible institutional officials.

5. **Monitoring.** The policy should specify procedures for internal, and, when deemed necessary, external monitoring when a financially interested individual is permitted to conduct human subjects research.

6. **Reporting by Covered Individuals.** The policy should require covered individuals to report to the institution all significant financial interests that would reasonably appear to be affected by the individual's current or anticipated human subjects research. In making such reports, each covered individual should be required to declare explicitly whether he or she does *or does not* have such financial interests; the failure to report is unacceptable.

    a. Reports should be required at least annually, with prompt updating whenever there is an interim, material change in significant financial interests.

    b. Some institutions currently require a researcher to indicate on the institutional face sheet accompanying the research proposal whether the researcher holds any significant financial interest in the research. All institutions should consider adopting this practice for research involving human subjects.

7. **Reporting to Supervisor.** When the COI committee determines that a financially-interested individual should be permitted to conduct human subjects research, a copy of the committee's summary report describing the financial interest and any conditions to be imposed upon the research should be provided to the head of the unit (e.g., department chair) in which the covered individual resides administratively, and to the responsible dean, provost, CEO, or other official who has institutional responsibility for monitoring the activities of the covered individual.

8. **Investigator Certification to IRB.** When a research proposal is submitted to the IRB for review, including continuing review (where applicable), each covered individual who will conduct the research should attest in writing to the IRB that financial report information on file for that individual is current and will be updated promptly to reflect relevant changes in financial circumstances. The IRB should forward any information that it receives concerning a significant financial interest in human subjects research to the COI committee.

9. **COI Committee Review of Significant Financial Interest Created by Licensing Agreements.** Prior to executing a technology licensing agreement, the Office of

Technology Licensing must determine whether the agreement would create a significant individual financial interest in ongoing or proposed human subjects research, and if so, inform the institution's COI committee of the proposed terms of the agreement. The COI committee should either approve the conduct of the research by the individual who will hold the financial interest, subject to an appropriate monitoring plan, or determine that the individual may not conduct the research if he or she wishes to retain the financial interest.

10. Disclosure of Significant Financial Interests.

a. The policy should require disclosure of the existence of significant financial interests in human subjects research as follows: to state and federal officials, as required by statute or regulation; to research funders or sponsors; to the editors of any publication to which a covered individual submits a manuscript concerning the research;[17] and in any substantive public communication of the research results, whether oral or written.

b. If an institution participating in a multi-center trial has judged a financially-interested individual eligible to conduct human subjects research at its site, that fact should be made known to the Principal Investigator or Sponsor, and to the IRBs of other institutions participating in the trial.

c. Research consent forms should, as a matter of institution's COI policy, disclose the existence of any significant financial interest held by a covered individual who is conducting the human subjects research. The precise wording of disclosure in the consent form should be determined by the IRB, but should include an explanation of the fact that the financial interest in question has been reviewed by the COI committee, approved subject to committee oversight, and determined by both the committee and the IRB not to pose any additional significant risk to the welfare of research subjects or the integrity of the research.

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[17] Disclosure to journal editors should take the form of an affirmative statement on behalf of each covered individual who conducted the research that he or she either does or does not hold significant financial interests in the research. This requirement is consistent with the recent uniform disclosure requirements published by a group of editors of major medical journals. F. Davidoff, C. D. DeAngelis, J.M. Drazen, et al. Sponsorship, authorship, and accountability. JAMA; 286;10:1232-1234.

[18] The National Human Research Protections Advisory Commission has recommended this approach to the disclosure of researchers' financial interests to research subjects. Letter from Mary Faith Marshall, Ph.D., Chair, NHRPAC, to Assistant Surgeon General/Acting Principal Deputy Assistant Secretary for Health Arthur J. Lawrence, Ph.D., dated August 23, 2001.

d. If the institution's COI committee has authorized a financially interested individual to conduct human subjects research, the disclosure statement in the research consent form should indicate that additional information (to include the COI summary report describing the nature and amount of the financial interest) will be provided to research subjects upon request.[18]

11. **Prohibition on Payments for Results.** The policy should prohibit payments from the institution or the sponsor to a covered individual, if such payments are conditioned upon a particular research result or are tied to successful research outcomes. Payments for subject enrollment or for referral of patients to research studies should be permitted only to the extent that such payments:

    a. Are reasonably related to costs incurred, as specified in the research agreement between the sponsor and the institution;

    b. Reflect the fair market value of services performed; and

    c. Are commensurate with the efforts of the individual(s) performing the research.

12. **Affirmation of Institutional Policies on Intellectual Property and Publication Rights.** The COI policy should affirm an investigator's accountability for the integrity of any publication that bears his or her name. The policy should also affirm the right of a principal investigator to receive, analyze, and interpret all data generated in the research, and to publish the results, independent of the outcome of the research. Institutions should not enter, nor permit a covered individual to enter, research agreements that permit a sponsor or other financially interested company to require more than a reasonable period of pre-publication review,[19] or that interfere with an investigator's access to the data or ability to analyze the data independently.[20]

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[19] For sponsored research, a reasonable period of review would be no more than 90 days, unless both parties agree that extenuating circumstances require an extension of time. The Task Force notes that for research involving NIH-funded research tools, the NIH has stated that it would consider a 30-60 day review period to be reasonable. National Institutes of Health, Principles and Guidelines for Recipients of NIH Research Grants and Contract on Obtaining and Disseminating Biomedical Research Resources, 64 Fed. Reg. 246, 72090 (Dec. 23, 1999).

[20] When research involves more than one institution and numerous investigators (e.g., a multi-center trial), the investigators may delegate primary authorship to a subset who will take responsibility for the publication.

13. **Protection of Students and Trainees.** Commercially sponsored research may give rise to financial incentives that conflict with a supervising researcher's responsibility to foster the academic development of students and trainees. Agreements with sponsors or financially interested companies that place restrictions on the activities of students or trainees or that bind students or trainees to non-disclosure provisions should ordinarily be prohibited. When deemed unavoidable, such agreements should be subjected to close scrutiny by the responsible university official and the institution's COI committee, and should be fully disclosed to all students and trainees prior to their involvement in the research. Under no circumstance should a student or trainee be permitted to participate in research if the terms and conditions of participation would prevent him or her from meeting applicable institutional degree requirements (e.g., completion and public defense of a thesis or dissertation). The institution's policy on financial interests in research should reaffirm, or explicitly cross-reference, the relevant institutional documents that address these matters.

14. **Legal Obligations.** The policy documents should alert covered individuals to all state and federal requirements applicable to financial interests in research, including state financial disclosure laws (if applicable), state licensure and professional conduct standards relevant to conflict of interest, federal laws relative to "finders fees" for research subjects, and SEC prohibitions against insider trading. The policy should also direct investigators who conduct FDA-regulated research to familiarize themselves with FDA policies concerning promotional activities.

15. **Sanctions.** The policy should define the range of possible sanctions for non-compliance, up to and including dismissal. The policy should reference the procedures to be followed for sanctioning violations and for appealing adverse determinations.

C. Policy Implementation

1. **Information Flow.** Institutions should implement policies, procedures, and systems that will facilitate prompt reporting of significant financial interests to the institution and enable the timely flow of accurate and complete information to and from the COI committee, the responsible IRB(s), the institutional Office of Technology Licensing, and responsible institutional officials.

2. **Electronic Reporting Form.** To enhance the efficiency of the reporting process, institutions should consider adopting an electronic disclosure form and permitting covered individuals to make and update financial reports on-line and in real time.

3. **Resources.** Implementation of a comprehensive, effective COI policy may require institutions to devote new resources to their compliance effort. Institutions should ensure that adequate resources and personnel are allocated to support effective, credible oversight of financial interests in human subjects research.

4. **Written Acknowledgement Required.** Institutions should require that all individuals who conduct human subjects research read and acknowledge in writing that they understand and agree to comply with the institution's COI policies.

5. **Education and Training.** Institutions should adopt mechanisms for disseminating COI policies to all faculty, staff, students, and trainees, and for providing appropriate education and training in these policies.

6. **Compliance Monitoring.** Institutions should regularly assess compliance with COI policies through the use of internal audit mechanisms and other appropriate self-evaluation strategies.

7. **Accreditation.** The effectiveness of COI policies and a formal assessment of institution-wide compliance with these policies should be examined as an element of any accreditation process for the institution's human subjects protection program.

Epilogue

During the past two decades, remarkable advancements in biomedical research and the stimulus of the Bayh-Dole Act have vastly increased the breadth and depth of engagement of academic medicine with industry. The growth of the biotechnology industry is a celebrated accomplishment of the U.S. economy during the second half of the 20th century, and together with the information technology industry has spurred public perception of research universities as engines of economic development and social betterment. But at the same time, the public insists that universities remain unblemished by financial self-interest and continue to serve society as trusted and impartial arbiters of knowledge. This "conflict of public expectations" is nowhere more intense than in academic medicine and in research involving human subjects, where the steadily deepening engagement of clinical research with the world of commerce is seen by many influential observers as threatening both research integrity and the welfare of research participants.

The Task Force acknowledges the enormous benefits that have inured to the public from the commercial development of medical inventions made in academic medical centers and anticipates that the relationships of these centers with industry will only continue to deepen in an era in which terms like genomics, proteomics, and physiomics are becoming commonplace. But the Task Force also recognizes that the public's extraordinary support of academic biomedical research will remain critically dependent upon public confidence and trust that are especially vulnerable in research involving human subjects. This is the reality, and it must be appreciated by industry as much as by academe if their future interactions are to thrive.

This first report from the AAMC Task Force on Financial Conflicts of Interest in Clinical Research deals with individual financial interests. It intends to raise the standards of institutional oversight and management of financial conflicts of interest, and make them more uniform across academic medicine. The report respects institutional autonomy: the recommended policy and guidance provide a floor that permits institutions to adopt even more stringent provisions if they wish. The report eschews a "one size fits all approach:" it recognizes that each case of potential financial conflict of interest in research must be closely examined on its merits, and must respect the particular institutional, individual, and scientific circumstances that may attend it.

The Task Force does not believe, and does not intend, that adoption of the recommended policy and guidelines by the academic medical community should interfere with healthy academic- industry relationships or with the continued robust flow of academic biomedical invention into beneficial products. The Task Force does believe that these policies and guidance can help to ensure that the relationships remain principled, protective of research subjects and scientific integrity, and capable of withstanding intense public scrutiny.