

Protecting Patients, Preserving Integrity, Advancing Health: Accelerating the Implementation of COI Policies in Human Subjects Research

A Report of the AAMC-AAU Advisory Committee on Financial Conflicts of Interest in Human Subjects Research

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Tomorrow's Doctors, Tomorrow's Cures®



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Table of Contents

Executive Summary	v
Introduction	1
Chapter 1: Policies on Individual Financial Conflicts of Interest in Human Subjects Research	5
Chapter 2: Policies on Institutional Financial Conflicts of Interest in Human Subjects Research	13
Chapter 3: Implementation of Conflicts of Interest Policies	22
APPENDIX A: Model Policy on Institutional Conflict of Interest in Human Subjects Research	36
APPENDIX B: Analyzing Cases Involving Potential Conflicts of Interest in Human Subjects Research: Template and Compendium of Cases	43
APPENDIX C: Definition of Financial Interests in Research	67
APPENDIX D: Institutional Policies and Practices on Consulting: Topics and Question to Consider	68
APPENDIX E: Advisory Committee Roster	70

Executive Summary

The vitality and integrity of biomedical research are critical to the health of the public and to finding the keys to addressing some of society's most compelling and difficult challenges. In the United States, universities and medical schools, the dominant source of this research, are now more than ever key components of the social, economic and scientific forces that empower our nation in a globalized economy. The academic research community is increasingly aware of pressures created by these changed societal expectations, particularly those associated with its relationships with industry. A principled partnership between the academic community and industry is essential if we are to realize the promise of biomedical research, but such collaboration can also create serious conflicts of interest. These pressures compel academic institutions to reaffirm their highest values of protecting the integrity of their research, the well being of the human subjects who participate in it, and the trust of the public.

The federal government has regulated financial conflicts of interest in federally sponsored research since 1995 while giving considerable deference to university policies. Recognizing that this deference rests critically on the trustworthiness and accountability of academic institutions, the Association of American Medical Colleges (AAMC) and the Association of American Universities (AAU) issued strong recommendations in 2001 and 2002 addressing individual and institutional financial conflicts of interest in research. In September 2005, in the wake of conflict of interest scandals that rocked the NIH, the Associations organized a workshop of senior university and medical center officials to address the question of whether the academic biomedical research community might benefit from more precise guidance on how to handle cases where conflicts arise among personal and institutional priorities and values.

Based on the advice received at that workshop, the Associations in 2006 charged a newly formed Advisory Committee with reviewing, and amplifying as appropriate, the Associations' previously-issued guidance on conflicts of interest in human subjects research. The Committee was asked to define the key issues confronting the biomedical research community, to develop a more nuanced stratification of the risks and benefits, to provide detailed guidance about the analysis and management of conflicts of interest, and to provide practical tools to ensure that academic research continues to be conducted in conformity with the institutions' core values.

The Advisory Committee, comprised of senior officials at major research universities and medical schools, met three times between January 2007 and January 2008; most of its work was accomplished electronically through three working groups. The Committee's Report addresses the predominant areas of concern in the identification, analysis, and management of conflicts of interest in human subjects research and presents an array of policy recommendations, as well as educational guidance and management tools, to assist institutions in dealing more effectively with the challenges raised by conflicts of interest. The three chapters of the report focus, respectively, on policies on individual conflicts of interest, policies on institutional conflicts of interest, and implementation of conflicts management programs.

While these recommendations are refinements of the basic principles expressed in the 2001 and 2002 AAMC and AAU guidance, the Committee strongly advocates the adoption of more consistent policies and practices across academic institutions. The Committee also asserts that time is of the essence with respect to fully implementing comprehensive conflicts of interest programs in human subjects research.

Chapter 1: Policies on Individual Financial Conflicts of Interest in Human Subjects Research

The first chapter, Policies on Individual Financial Conflicts of Interest in Human Subjects Research, recommends refinements of the existing guidance from the Associations in three key areas: the definition of covered individuals, the meaning of “compelling circumstances,” and the expansion of reporting and disclosure of conflicts of interest. Additional recommendations grew out of the Committee’s consideration of variability of practices in the academic community and concern about inconsistencies in policies across institutions.

A. Covered Individuals

NIH’s recent Targeted Site Review of 18 grantee institutions revealed that some of the institutions’ interpretations of those covered by PHS regulations were inconsistent with and were narrower than NIH’s interpretation. Accordingly, the Advisory Committee recommends a definition of “covered individual” that is consistent with that of NIH.

Recommendation: *Based on NIH’s determination that role rather than title should control, institutions should adopt in their own conflicts of interest policies the regulation’s broader interpretation of covered individuals. That is, a covered individual for purposes of an institution’s policy on individual conflicts of interest should be the following: the principal investigator and any other person who shares responsibility for the design, conduct, or reporting of funded research, and the spouse and dependent children of the investigator and any other person who shares such responsibility.*

B. Compelling Circumstances

The 2001 AAMC Report recommended that institutions adopt a rebuttable presumption against participation in human subjects research by a conflicted investigator that could be overcome only by a showing of “compelling circumstances.” Experience with implementing the 2001 recommendation demonstrated a need for additional explanation of what “compelling circumstances” might mean.

Recommendation: *(a) Early-stage research: In addition to the examples of compelling circumstances provided in the 2001 AAMC Report, experimentation to further develop an early stage discovery may similarly require the insights, knowledge, perseverance, laboratory resources, or special patient populations of the discoverer. The best interests of patients who could benefit from the discovery may justify further involvement of the discoverer as an investigator. If such circumstances are deemed compelling by the applicable conflicts of interest committee, the analysis should define the stages of the research and the specific activities for which there are compelling*

reasons for the conflicted discoverer/investigator's involvement, and an approved management plan should be structured to restrict the investigator's roles to those stages and activities. The management plan should include a clear discussion of the time line proposed for elimination of the conflicted investigator from research participation and the strategy to restrict the time of involvement of a conflicted investigator to a minimum.

Approval and management of the conflict may differ between experiments designed to promote further development on the one hand and those designed to validate claims linked to the discovery on the other. Approval of such research when human subjects are involved should require particularly stringent analysis of the degree of risk to subjects and of the effectiveness of particular provisions of the conflict management plan to protect subjects and prevent the introduction of bias of the conflicted investigator.

(b) Low risk research: In considering the degree of risk to human subjects, as called for in the 2001 Report, an institution's conflicts of interest committee may encounter human subjects studies in which careful assessment finds risk to human subjects to be sufficiently low that the disposition of any associated conflict by the committee may be similar or identical to the disposition that would be made by that institution in non-human subjects research.

C. Reporting of Potential Conflicts of Interest

The Advisory Committee determined that reporting of financial interests by researchers to their institutions should be clarified and expanded to reduce the possibility of inadvertent failure to comply with reporting requirements and to better assure consistent standards of "relatedness" of reported financial interests to particular research projects.

Recommendation: *The requirement for reporting a covered individual's outside financial interests that are directly or indirectly related to professional responsibilities to the institution should be extended to eliminate any de minimis threshold.*

However, the PHS de minimis thresholds may continue to be used to define significant financial interest for the purpose of applying the rebuttable presumption against participation by a conflicted investigator in human subjects research.

An institution may wish to consider exempting certain clearly defined types of consulting and fees from its definition of reportable financial interests, e.g., fees for serving on grant review committees (study sections), and fees given as honoraria by another academic institution for an academic activity, such as a seminar or grand rounds presentation.

Recommendation: *Covered individuals performing human subjects research should be required to report all of their outside financial interests directly or indirectly related to their professional responsibilities to the institution, including their dollar amount, whether or not the individual believes these financial interests might reasonably appear to be affected by the individual's current or anticipated human subjects research.*

The policy established by the institution should indicate to the reporting individuals how and to what extent their financial information will be handled and shared by the institution.

D. Pre-Clinical Research

The Advisory Committee believed that certain pre-clinical research may warrant special attention where there is a reasonable anticipation of follow-on human subjects research in the immediate future.

Recommendation: *With respect to pre-clinical research, institutions should consider requiring covered individuals to indicate if their current non-human subjects research that is linked to any of their reportable financial interests is reasonably anticipated (1) to be a component of an IND submission or (2) to progress to research involving human subjects within the coming 12 months. In such circumstances, the institution's conflicts of interest committee should have the authority to decide whether any of the policy stipulations that apply to human subjects research should apply to this "pre-clinical" stage of the individual's research.*

E. Disclosure of Potential Conflicts of Interest

The Committee emphasized the importance of broadening the scope of disclosure of managed conflicts of interest both inside and outside the institution.

Recommendation: *Disclosure should be extended both in scope and in audience, to assure full awareness of potential conflicts and institutional efforts to address them. Specifically, an institution's policy should require, with respect to any human subjects research project, disclosure of the existence of all financial interests of a covered individual that are related to that human subjects research project as follows: to state and federal officials, as required by statute or regulation; to research funders or sponsors; to all of the researchers, students, and trainees at the institution working with the covered individual on the research project in question; to the editors of any publication to which a covered individual submits a manuscript concerning the research; in any substantive public communication of the research results, whether oral or written; and to the human subjects of the research project, as specified below. Substantive public communication of the research results includes presentations to or interchanges with the media, and applies whether the audience is lay persons or other professionals.*

Institutional policies should provide that the disclosures referenced above should generally be sufficiently specific to indicate whether the financial interest is an arrangement including but not limited to (i) consulting or other fees, (ii) royalties, (iii) stock, equity or stock options, (iv) an institutionally-defined inventor's share, (v) a board or other position with advisory or fiduciary duties, (vi) another type of arrangement, which would be indicated, or a combination of these. Generally, such disclosures should also indicate that the conflict has been reported to and is being managed by the institution.

With respect to disclosure to human subjects in research consent forms, and as is indicated in the 2001 AAMC Report, "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 to the integrity of the research."

For the purpose of this Recommendation, the document or statement by which disclosure is made need not itself contain all the information referenced above, on condition that the disclosure includes a clear reference to the presence of the conflicting interest, an indication that additional information is available regarding the details of the conflicting interest and how it is being managed, and how that information can be readily obtained by those to whom the disclosure is made.

F. IRB Responsibilities Relating to Conflicts of Interest

The Advisory Committee gave special attention to potential conflicts of interest of IRB members.

Recommendation: *Institutions should have clear policies, compliant with applicable federal regulations that address the reporting and management of conflicts of interest of IRB members. The provisions should require reporting of all financial interests (no de minimis threshold) by IRB members, in the same manner as is required for investigators, upon their initial appointment to the IRB, with updating annually and more often when circumstances change. The provisions should specify how the IRB Chair and/or the Administrator of the IRB will identify and evaluate potential conflicts of interest of IRB members and make clear that any conflicted IRB member must be recused from any deliberations relating to studies with which that IRB member has a potential conflict of interest.*

The remaining recommendations in this Chapter, though not specifically focused on provisions of policies on conflicts of interest in human subjects research, address three issues that the Committee believed merited special attention: inter-institutional variations in policies and practices regarding conflicts of interest, conflicts of interest in clinical practice, and the responsibility of national associations in educating the public on the importance of academic-industry relationships and the manner in which conflicts of interest are addressed by academic institutions.

G. Institutional Variations in Conflicts of Interest Policies and Practices

Recommendation: *While there are clear advantages to having somewhat uniform guidelines and policies for conflicts of interest in clinical research, universities and academic medical centers vary in many ways, including in their institutional cultures, traditions, missions and objectives, as well as in the populations they serve. The Advisory Committee thus endorses the statement on institutional variations in the 2001 AAMC Report, but strongly advises against variations that lead to standards less rigorous than those set forth in this Report.*

H. Conflicts of Interest in Clinical Practice

Recommendation: *Institutions should adopt policies and establish standards that minimize bias in the practice of medicine due to real or perceived conflicts of interest of their medical faculty.*

I. Educating the Public, the Government, and the Media Regarding Avoidance and Management of Conflicts of Interest While Supporting Innovation in Clinical Research

Recommendation: *The Advisory Committee recognizes the benefit to the public in general, and to the patient populations of our academic medical centers in particular, of the translation of research into new therapies, devices, and disease-preventing strategies. The Committee also recognizes the substantial public benefits that would accrue from improving understanding of the ways in which research is funded, and of the extensive management procedures that are focused on potential conflicts of interest in human subjects research in order to avoid or limit any potential adverse effects from the conflicts.*

Therefore, the Committee strongly urges the AAMC, the AAU, and other professional organizations to take responsibility for developing and implementing strategies to educate the public, the media, and the government on the value of academic-industry relationships, and on how academic medical centers apply their conflicts of interest policies to protect the safety of human research subjects and the integrity of clinical research. Such educational strategies need to be implemented on a continuing basis over the long term and should not be confined to episodic responses to instances of public concern.

Chapter 2: Policies on Institutional Financial Conflicts of Interest in Human Subjects Research

The second chapter, Policies on Institutional Financial Conflicts of Interest in Human Subjects Research, supplements the Associations' previously-issued guidance. Institutional conflicts of interest are a source of growing concern as the number and complexity of the roles played by institutions of higher education continue to increase, and their relationships with industry continue to expand. At the same time, and notwithstanding the earlier guidance documents, the development and implementation of comprehensive institutional conflicts of interest policies continues to challenge the academic community. Based on this experience, the Committee addressed many of the especially difficult institutional conflicts of interest issues, and its Report offers a template for a policy on institutional conflicts of interest in human subjects research (Appendix A). The template is not offered as *the* model policy but rather as an example of how an institution might choose to address the topics identified in this chapter. The Committee's recommendations follow.

A. Development and Adoption of Policies

Although the Advisory Committee was charged with examining institutional conflicts of interest specifically in the context of human subjects research, the Committee urged AAU and AAMC member institutions to commit themselves to develop and implement comprehensive institutional conflicts of interest policies that govern all operational aspects of a university or an academic medical center. Its recommendation on policies addressing institutional conflicts of interest in human subjects research is the following.

Recommendation: *The Advisory Committee recommends that all AAU institutions and AAMC schools of medicine and teaching hospitals should:*

- a. develop an institutional COI policy covering both the financial interests of the institution and of institutional officials, including deans, department chairs and division chiefs, in human subjects research;
- b. implement an institutional COI reporting, evaluation, and management process, and create an objective and credible institutional COI review process involving a standing internal committee or an external review entity. Irrespective of their structures, these entities must be empowered to inform institutional leadership and decision-making;
- c. complete policy development and implementation within two years of issuance of this report.

B. Separation of Administrative Responsibility

The Committee reiterated the key structural element of effective institutional conflicts of interest programs, management separation, which was initially articulated in the earlier AAMC and AAU guidance.

Recommendation: *Research and financial decision-making processes and agents must be separated.*

C. Rebuttable Presumption

Also carried forward from the earlier AAMC and AAU guidance, this recommendation represents the other key principle in responsible institutional conflicts of interest programs, that a rebuttable presumption should be established for institutional conflicts of interest in human subjects research.

Recommendation: *Decisions about whether or not to pursue a particular human subjects research project in the presence of an institutional conflict of interest should be governed by a “rebuttable presumption” against doing the research at or under the auspices of the conflicted institution.*

D. Consistent Implementation

The Advisory Committee believed that it is necessary to the credibility of any institutional conflicts of interest program that the institution and its officials be held to high standards and that the standards be consistently applied.

Recommendation: *Institutions should ensure in policy and practice that institutional COIs will be addressed consistently throughout the institution, such that those subject to institutional financial conflict of interest policies, specifically officials of the institution and the institutions themselves, are subject to substantive reporting, disclosure, and management of their financial interests to protect the integrity of human subjects research and the subjects who participate in it, as well as institutional values and decision-making.*

E. Institutional COI Committee

This recommendation clarifies that the committee structure that is put into place for addressing institutional conflicts of interest may be the same as that for individual conflicts of interest.

Recommendation: *Institutions should form a standing institutional COI Committee to review and analyze potential institutional COIs. [Note that institutions may choose to use for this purpose the committee established to address individual COI.] The Committee must be able to analyze when it would be appropriate and in the public interest to accept and manage a conflict, rather than require that it be eliminated.*

All recommendations and considerations pertinent to institutional policy development are incorporated into the template policy. In this manner, the Advisory Committee hopes to ease the task of developing and implementing institutional conflicts of interest policies for those institutions that have not done so and of refining existing policies for those institutions that have.

Chapter 3: Implementation of Conflicts of Interest Policies

The third chapter, Implementation of Conflicts of Interest Policies, offers specific, practical advice on putting conflicts of interest policies into practice. The Chapter provides a detailed discussion of how to analyze conflicts of interest cases as well as guidance on key elements of conflicts of interest programs. The discussion is supplemented by a short-form template for analysis of conflicts of interest cases and by ten detailed case studies based on real situations at several research intensive universities and medical schools. The cases illustrate the complexity of conflicts of interest and the application of the analysis template to particular fact patterns. The Advisory Committee considers the compilation of cases a work in progress and has asked the AAMC to continue to build upon and update it. The Committee commends the use of the cases as teaching tools for probing key questions that are implicated when conflicts of interest are present.

The observations and suggestions in this chapter are based on the assumption that many inconsistencies and perceived shortcomings across institutions in addressing research-related conflicts of interest may result from the lack of widely accepted templates for doing so. The Advisory Committee believes that adequate education of faculty and staff in all aspects of individual and institutional conflict of interest policies and processes is essential to safeguard the integrity and vitality of the institution and its research and teaching activities, and to assure the principled nature of the institution's relationships with its industry partners. The following topics are addressed in detail in Chapter 3:

- Analysis of cases involving potential conflicts of interest in clinical research;
- Management of conflicts of interest;
- Monitoring conflicts programs and management of conflicts;
- External professional activities and consulting;
- Education.

The detailed steps presented under these topic headings constitute a model for institutions to approach more systematically the analysis and management of conflicts of interest, and they cumulatively represent a set of recommendations and standards for responsible and effective conflicts of interest programs. In addition, Chapter 3 contains one formal recommendation specifically focusing on education of the research community.

Recommendation: *Through its Forum on Conflicts of Interest in Academe, the AAMC should update and supplement the case studies on a continuing basis and make them available on appropriate websites in order that they may continue to be useful to the research community as means for teaching about conflicts of interest in human subjects research. The AAMC should also make broadly available other quality teaching tools that have been developed by particular institutions on conflicts of interest.*

Conclusion

The Advisory Committee recognized two fundamental problems in the current state of affairs in conflicts of interest programs. The first is the lack of consistency across academic institutions in the standards for addressing research-related conflicts of interest. The other problem involves the tension in the culture of today's academic institutions, where steadily mounting pressure to participate in economic development and technology transfer technology may conflict with fundamental academic values. The Advisory Committee believes that its Report offers practical ways in which the academic community can address these issues vigorously, responsibly, and in keeping with their commitment to the integrity of research, the protection of human subjects, and the preservation of public trust.

Introduction

The vitality and integrity of biomedical research are critical to the health of the public and to finding the keys to addressing some of society's most compelling and difficult challenges. In the United States, universities and medical schools, the dominant source of this research, are now, more than ever, essential parts of the social, economic and scientific forces that empower nations in a global world.

Consistent with this new role for academic institutions, the past thirty years have brought about a major cultural shift in research universities, and especially in medical schools, with respect to faculty activities. Where once the development of products for the marketplace was discouraged and even looked down upon by research faculty, scientists today are encouraged to share their expertise with industry through consulting, speaking, or other arrangements, to collaborate with industry in product development, and to form their own companies.

The Bayh-Dole Act of 1980 accelerated this shift by allowing faculty and institutions to retain title to the intellectual property resulting from their federally supported research and by encouraging them to promote the commercial development of their discoveries through technology licensing. There can be no doubt that Bayh-Dole has been an unparalleled success in speeding discoveries from the laboratory to the marketplace, resulting in great social benefit. Indeed, the December 12, 2002 *Economist* referred to Bayh-Dole as “possibly the most inspired piece of legislation to be enacted in America over the last half-century.”

However, the benefits of Bayh-Dole and the broader roles of the academic community have come with some potential downsides, and the risks to the integrity of the research mission of academic institutions and their faculty in this new paradigm are decidedly higher. The promises of translational research, the challenges of technology transfer, and intense expectations at all levels of government that universities and their academic medical centers function as engines of socio-economic development generate new pressures on institutions and their faculty members to expand their relationships and deepen their engagement with industry. These relationships, now encouraged in many forms, may involve financial linkages that are entirely benign but will in other cases carry the potential to create serious conflicts of interest. Moreover, these financial ties are occurring in a context of dramatically increased public sensitivity to and concern with allegations of financial conflicts of interest more broadly in university business transactions and across diverse sectors of industry.

In recognition of these changing circumstances, both the federal government and the academic community have been active in defining their respective responsibilities to assure the integrity of these commercial relationships. The federal government has regulated financial conflicts of interest in federally sponsored research since 1995 while giving considerable deference to university policies. Recognizing that this deference rests critically on the trustworthiness and accountability of academic institutions, the Association of American Universities (AAU) and the Association of American Medical Colleges (AAMC) separately and together have been addressing conflicts of interest policies and practices for more than two decades.

In 2001 and 2002, each association issued strong recommendations to its member institutions for developing policies and procedures for the oversight and management of individual and institutional conflicts of interest.¹

In response, the academic community has adopted costly programs and procedures to adapt its policies and practices to these recommendations, as part of a continuing process of identifying and acting upon the challenges and opportunities presented by their relationships with industry. A survey conducted by the AAMC three years after the recommendations were issued confirmed that the academic community has taken them seriously, especially those that address *individual* financial conflicts of interest, and has attempted to bring its institutional policies into conformity.² With respect to *institutional* financial conflicts of interest, however, more recent survey data indicate that the community continues to struggle with these very complex and challenging issues.³

Although these efforts have been substantial and sustained, issues concerning conflicts of interest within the academic research community continue to arise. A recent report from the NIH of site visits to 18 of its top-ranked awardee institutions noted that although the institutions demonstrated a “solid awareness” of the importance of compliance with federal conflict of interest regulations, some of them have not been consistently diligent in timely reporting instances of financial conflicts of interest to the agency as required by the regulations.⁴ In response to that report, the U.S. Department of Health and Human Services Office of Inspector General has investigated and sharply criticized the NIH’s performance of its regulatory oversight responsibilities, and has issued recommendations that call for detailed reporting of financial conflicts of interest cases to the agency by awardees. These recommendations underscore yet again how lapses by awardee institutions in fulfilling their commitments in research oversight engender distrust and erode confidence in the ability of the community to manage these issues responsibly on their own.

Integrity of research, the protection of human research subjects, and the preservation of public trust are paramount values of academic culture. Yet, due to their deepening engagement with the commercial sector, faculty and institutions face conflict of interest challenges that were scarcely imaginable even a decade

¹ Association of American Medical Colleges, Task Force on Financial Conflicts of Interest in Clinical Research: *Protecting Subjects, Preserving Trust, Promoting Progress—Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research* (December 2001). Association of American Universities, Task Force on Research Accountability: *Report on Individual and Institutional Financial Conflict of Interest* (October 2001). Association of American Medical Colleges, Task Force on Financial Conflicts of Interest in Clinical Research: *Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of an Institution’s Financial Interests in Human Subjects Research* (October 2002).

² Ehringhaus SH and Korn D, *US Medical School Policies on Individual Financial Conflicts of Interest. Results of an AAMC Survey* (September 2004).

³ Ehringhaus SH, Weissman JS, Sears JL, et al. Responses of Medical Schools to Institutional Conflicts of Interest. *JAMA*.2008;299(6):665-671.

⁴ National Institutes of Health, Office of Extramural Research: *Observations from NIH’s FY 2006 Targeted Site Reviews on Financial Conflict of Interest*, (2/15/2007) <http://grants.nih.gov/grants/policy/coi/index.htm>.

ago. Accordingly, the associations resolved to examine the extent to which current conflict of interest policies and management practices in higher education and academic medicine continue to conform to the institutions' core values and justify continued public confidence in the integrity and credibility of academic research. The goal of this process is to strengthen and achieve better harmonization of the policies and practices by which the academic community defines, manages, and oversees potential individual and institutional conflicts of interest in biomedical research.

At least two fundamental problems have been identified in the current state of affairs. The first is a lack of consistency across academic institutions in the standards for addressing research-related conflicts of interest. While federal regulations allow considerable institutional flexibility in deference to unique institutional cultures, such cultural differences should never allow institutions and faculty to stray from the core principles of scientific integrity and protection of human research subjects, or to distort institutional responses to pressures that might bias research findings.

The other problem is the mixed message that pervades the culture of today's academic institutions. Faculty are acutely aware of the opportunities, incentives, and imperatives presented by the Bayh-Dole legislation as well as steadily mounting political pressure to transfer technology, enhance economic development, and increase ties between academic medicine and industry. Yet, these forces, while being acknowledged, must not be allowed to compromise the integrity of their research and teaching endeavors or encourage the perception that integrity has been compromised. In accommodating these sometimes competing priorities, institutional culture must continuously articulate and reinforce the overarching imperative of professional integrity by responsibly monitoring and addressing individual and institutional conflicts of interest at all levels of the institution that affect research.

To confront these problems, the AAU and the AAMC convened an Advisory Committee late in 2006 to develop more precise guidance on appropriate responses to those circumstances in which conflicting personal and institutional priorities and values commonly arise. The Committee agreed that review and, as appropriate, clarification and supplementation of the standards articulated in the earlier AAU and AAMC reports would help to strengthen and harmonize institutional protections even in the presence of cultural differences. Further, it would enable universities and academic medical institutions to weigh better the anticipated benefits of specific biomedical research proposals against the risks that specific individual and institutional financial relationships pose to research participants, scientific integrity, and the institution itself. Finally, such an effort could reassure the public that the intensifying emphasis on technology transfer and interactions with industry has not blunted academia's drive to create and transmit new knowledge based on scientific opportunity and societal need, its commitment to research integrity, and its paramount duty to protect human research subjects.

Accordingly, the Advisory Committee has examined the key issues confronting the biomedical research community in identifying and managing conflicts of interest in research, and, while ascertaining the continued validity of the associations'

principles and guidance, has recommended refinements and clarifications of the associations' previously published statements on these matters.

The report is divided into three chapters and contains a number of appendices. The first chapter, Policies on Individual Financial Conflicts of Interest in Human Subjects Research, recommends refinements of the existing association guidance in three key areas: the definition of covered individuals, the meaning of “compelling circumstances,” and the expansion of reporting and disclosure activities. In addition, it offers an additional recommendation on preclinical research.

The second chapter focuses on Policies on Institutional Financial Conflicts of Interest in Human Subjects Research and supplements previously issued guidance in this area by AAU (2001) and AAMC (2002), as well as by the Secretary of the Department of Health and Human Services (2004). In recognition of the difficulty that many institutions have faced in codifying institutional conflict of interest standards,⁵ the report also provides a template for an institutional conflict of interest policy (Appendix A).

The third chapter, Implementation of Conflicts of Interest Policies, offers specific guidance on practical aspects of putting conflicts of interest policies into practice. The chapter provides a detailed discussion of how to analyze conflicts of interest cases and provides guidance on the key elements of conflicts of interest programs. This discussion is supplemented by a short-form template for analysis of conflicts of interest cases, and by ten detailed case studies based on real situations at several research intensive universities and medical schools to illustrate the complexity of conflicts and the application of the analysis template to the fact patterns presented (Appendix B). These case studies will provide an invaluable teaching tool for faculty, research personnel, students, and other trainees by illustrating concretely the application of the policy provisions and questions that must be addressed.

The Advisory Committee believes that by developing and adopting nationally acceptable standards, supplemental guidance, and recommendations for responding to common conflicts of interest, the academic community should be better equipped to protect its core principles of research integrity, and to show more convincingly that its policies and practices are appropriate to its multi-faceted missions, and that the steps it takes to protect against conflicts of interest are serious, purposeful, transparent, and effective.

Although this report focuses on those conflicts that arise in the context of human subjects research conducted primarily within or under the supervision of medical schools and teaching hospitals or by their personnel, institutions should strongly consider making the principles and processes recommended in this report applicable to all research. Protection of integrity and public trust are indeed values that underpin all academic research, irrespective of whether the particular challenges associated with human subjects research are present.

⁵ Boyd EA, Lipton S, and Bero L. Implementation of Financial Disclosure Policies to Manage Conflicts of Interest. How seven Universities of California campuses deal with their research relationships. Health Tracking, March/April 2004.

Chapter 1

Policies on Individual Financial Conflicts of Interest in Human Subjects Research

A. Clarification of Individual Financial Conflicts of Interest Policies

The AAMC and the AAU endorse their statements issued in 2001 and 2002 regarding policies on individual and institutional financial conflicts of interest.⁶ Several areas, however, are in need of clarification and refinement. This chapter focuses on policies on individual financial conflicts of interest (COI).

1. Covered Individuals

Since the adoption of the Public Health Service (PHS) regulations on Objectivity in Research in 1995 (42 CFR Part 50 Subpart F), different practices have developed in the academic community regarding the applicability of the regulations to research personnel other than the principal investigator on a PHS-funded project. Those differences became especially apparent during the National Institutes of Health (NIH) 2006 Targeted Site Review program, an NIH initiative that focused specifically on assessing institutional compliance with the regulations as they pertain to NIH grants. Though the institutions that participated in the reviews were found to have implemented the regulations “thoughtfully and with diligence,” NIH observed that some institutions define “investigator” too narrowly.⁷

The regulation defines “investigator” as the principal investigator and any other person who is responsible for the design, conduct, or reporting of funded research, and it includes the investigator’s spouse and dependent children (42 CFR § 50.603). On the basis of its site review visits NIH reminded institutions that the PHS definition of investigator is very broad, and that it is incumbent upon them to determine which individuals are subject to the financial conflict of interest regulations. Accordingly, NIH urged institutions to consider the roles, rather than the titles, of those involved in research and the degree of independence with which those individuals work. “When the definition of investigator is limited to titles or designations (e.g., to principal investigators, key personnel, faculty) the risk that an unidentified financial conflict of interest may compromise the research enterprise increases.”⁸ NIH has taken the position that the term “covered individual” includes the spouse and dependents not only of the principal investigator but also of any other person who shares responsibility for the design, conduct, and reporting of research.

⁶ The AAU and AAMC reports are available on the Association websites at aau.edu and aamc.org.

⁷ National Institutes of Health, Office of Extramural Research: *Observations from NIH’s FY 2006 Targeted Site Reviews on Financial Conflict of Interest*, (2/15/2007) <http://grants.nih.gov/grants/policy/coi/index.htm>.

⁸ *Ibid.*

Recommendation: *Based on NIH’s determination that role rather than title should control, institutions should adopt in their own conflicts of interest policies the regulation’s broader interpretation of covered individuals. That is, a covered individual for purposes of an institution’s policy on individual conflicts of interest should be the following: the principal investigator and any other person who shares responsibility for the design, conduct, or reporting of funded research, and the spouse and dependent children of the investigator and any other person who shares such responsibility.*

2. Compelling Circumstances

The 2001 AAMC Report was built on an analytical framework that posited a rebuttable presumption against participation by a conflicted investigator in research on human subjects. However, that presumption could be overcome under certain circumstances so that it would be possible to permit a researcher to continue involvement in a research project despite the presence of a clear conflict of interest, where the impacts of the conflict could be adequately managed.

The 2001 AAMC Report provided that:

“In the event of compelling circumstances, an individual holding significant financial interests in human subjects research may be permitted to conduct the research. Whether the circumstances are deemed compelling will depend in each case upon the nature of the science, the nature of the interest, how closely the interest is related to the research, and the degree to which the interest may be affected by the research. When the financial interest is directly related to the research and may be substantially affected by it, (e.g., an equity interest in a start-up company that manufactures the investigational product) the risk is greatest and the bar must be high; however, even direct and potentially lucrative financial interests may be justified in some circumstances. For example, when the individual holding such interests is uniquely qualified by virtue of expertise and experience and the research could not otherwise be conducted as safely or effectively without that individual, he or she should be permitted the opportunity to rebut the presumption against financial interests by demonstrating these facts to the satisfaction of an institution’s conflict of interest (COI) committee. The COI committee might approve the involvement of such an individual in the research, subject to conditions that ensure effective management of the conflict and credible oversight of the research.”⁹

Recommendation: *(a) Early-stage research: In addition to the examples of compelling circumstances provided in the 2001 AAMC Report, experimentation to further develop an early stage discovery may similarly require the insights, knowledge, perseverance, laboratory resources, or special patient populations of the discoverer. The best interests of patients who could benefit from the discovery may justify further involvement of the discoverer as an investigator. If such circumstances are deemed compelling by the applicable conflicts of interest committee, the analysis should define the stages of the research and the specific activities for which there are*

⁹ AAMC Task Force on Financial Conflicts of Interest in Clinical Research: *Protecting Subjects, Preserving Trust, Promoting Progress—Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research*, p.7.

compelling reasons for the conflicted discoverer/investigator's involvement, and an approved management plan should be structured to restrict the investigator's roles to those stages and activities. The management plan should include a clear discussion of the time line proposed for elimination of the conflicted investigator from research participation and the strategy to restrict the time of involvement of a conflicted investigator to a minimum.

Approval and management of the conflict may differ between experiments designed to promote further development on the one hand and those designed to validate claims linked to the discovery on the other. Approval of such research when human subjects are involved should require particularly stringent analysis of the degree of risk to subjects and of the effectiveness of particular provisions of the conflict management plan to protect subjects and prevent the introduction of bias of the conflicted investigator.

(b) Low risk research: In considering the degree of risk to human subjects, as called for in the 2001 Report, an institution's conflicts of interest committee may encounter human subjects studies in which careful assessment finds risk to human subjects to be sufficiently low, so that the disposition of any associated conflict by the committee may be similar or identical to the disposition that would be made by that institution in non-human subjects research.

Though all of the Cases provided in Appendix B illustrate risk benefit analysis and, to varying degrees, the operation of the compelling circumstances standard, the following represent examples of how the compelling circumstances standard might be applied under different fact patterns: Case 2, Part B; Case 3; Case 4, Part A; Case 5; and Case 6. Differing levels of risk are illustrated by Case 2, Part A (low); Case 3 (high); and Case 7 (high). How particular management strategies might be selected is illustrated by Case 2, Part A; Case 4, Part A; Case 5; Case 7, Part A; Case 9; and Case 10.

3. Reporting of Potential Conflicts of Interest

The AAMC 2001 Report distinguishes between “reporting” and “disclosing” conflicts of interest. “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).”¹⁰ “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).”¹¹

¹⁰ Ibid. p.12.

¹¹ Ibid. p.11.

The AAMC 2001 Report advises as follows on the subject of internal reporting within the institution:

“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.”¹²

Tracking the 1995 PHS regulation, the AAMC 2001 Report limited reporting by covered individuals to those financial interests that meet the definition of “significant.” In certain cases, “significant” was tied to a dollar *de minimis* amount established in the PHS regulation of \$10,000 (for consulting fees and other kinds of compensation and gifts) and more than \$10,000 and 5% ownership interest in a single entity.

Recommendation: *The requirement for reporting a covered individual’s outside financial interests that are directly or indirectly related to professional responsibilities to the institution should be extended to eliminate any de minimis threshold. (Please see Appendix C for the definition of “financial interests,” as provided in federal regulation but with de minimis amounts deleted.)*

However, the PHS de minimis thresholds may continue to be used to define significant financial interest for the purpose of applying the rebuttable presumption against participation by a conflicted investigator in human subjects research.

An institution may wish to consider exempting certain clearly defined types of consulting and fees from its definition of reportable financial interests, e.g., fees for serving on grant review committees (study sections), and fees given as honoraria by another academic institution for an academic activity, such as a seminar or grand rounds presentation.

The 2001 AAMC recommendation places a difficult burden on the covered individual to make the decision about which of his or her outside financial interests would reasonably appear to be affected by the individual’s current or anticipated human subjects research. This formulation almost certainly creates the potential for inconsistencies on the parts of individuals as to which of several interests are reportable. Accordingly, to promote accuracy and consistency, the responsibility

¹² Ibid. p.17.

for determining which financial interests are relevant to a determination of conflict of interest should shift to the institution.

Recommendation: *Covered individuals performing human subjects research should be required to report all of their outside financial interests directly or indirectly related to their professional responsibilities to the institution, including their dollar amount, whether or not the individual believes these financial interests might reasonably appear to be affected by the individual's current or anticipated human subjects research.*

The policy established by the institution should indicate to the reporting individuals how and to what extent their financial information will be handled and shared by the institution.

This formulation recognizes that individuals may have outside financial interests that are unrelated to their professional competence, e.g., that do not relate to their role as a researcher. It also enables the institution to make accurate and consistent judgments as to whether a particular financial interest creates a potential conflict of interest.

Recommendation: *With respect to pre-clinical research, institutions should consider requiring covered individuals to indicate if their current non-human subjects research that is linked to any of their reportable financial interests is reasonably anticipated (1) to be a component of an IND submission or (2) to progress to research involving human subjects within the coming 12 months. In such circumstances, the institution's conflicts of interest committee should have the authority to decide whether any of the policy stipulations that apply to human subjects research should apply to this "pre-clinical" stage of the individual's research.*

4. Disclosure of Potential Conflicts of Interest

Unlike reporting, which focuses on internal provision of information to the institution about covered individuals' financial interests, disclosure relates to the release of relevant information about financial interests in particular human subjects research projects to parties outside the institution's COI review and management process. The 2001 AAMC Report addresses the issue of disclosure of the existence of significant financial interests in human subjects research as follows: "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; and in any substantive public communication of the research results, whether oral or written."¹³

¹³ Ibid. p.18.

It is important to note that while the Advisory Committee recommends that covered individuals report to the institution all financial interests related to their professional competence, the Committee recommends that for purpose of *disclosure with respect to any given research project*, disclosure is limited to those financial interests *that relate to that research project itself*.

Recommendation: *Disclosure should be extended both in scope and in audience, to assure full awareness of potential conflicts and institutional efforts to address them. Specifically, an institution’s policy should require that, with respect to any human subjects research project, disclosure of the existence of all financial interests of a covered individual that are related to that human subjects research project as follows: to state and federal officials, as required by statute or regulation; to research funders or sponsors; to all of the researchers, students, and trainees at the institution working with the covered individual on the research project in question; to the editors of any publication to which a covered individual submits a manuscript concerning the research; in any substantive public communication of the research results, whether oral or written; and to the human subjects of the research project, as specified below. Substantive public communication of the research results includes presentations to or interchanges with the media, and applies whether the audience is lay persons or other professionals.*

Institutional policies should provide that the disclosures referenced above should generally be sufficiently specific to indicate whether the financial interest is an arrangement including but not limited to (i) consulting or other fees, (ii) royalties, (iii) stock, equity or stock options, (iv) an institutionally-defined inventor’s share, (v) a board or other position with advisory or fiduciary duties, (vi) another type of arrangement, which would be indicated, or a combination of these. Generally, such disclosures should also indicate that the conflict has been reported to and is being managed by the institution.

With respect to disclosure to human subjects in research consent forms, and as is indicated in the 2001 AAMC Report, “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 to the integrity of the research.”¹⁴

For the purpose of this Recommendation, the document or statement by which disclosure is made need not itself contain all the information referenced above, on condition that the disclosure includes a clear reference to the presence of the conflicting interest, an indication that additional information is available regarding the details of the conflicting interest and how it is being managed, and how that information can be readily obtained by those to whom the disclosure is made.

¹⁴ Ibid. p.18.

5. IRB Responsibilities Relating to Conflicts of Interest

The following additional provisions should be codified in institutional policy.

Recommendation: *Institutions should have clear policies, compliant with applicable federal regulations that address the reporting and management of conflicts of interest of IRB members. The provisions should require reporting of all financial interests (no de minimis threshold) by IRB members, in the same manner as is required for investigators, upon their initial appointment to the IRB, with updating annually and more often when circumstances change. The provisions should specify how the IRB Chair and/or the Administrator of the IRB will identify and evaluate potential conflicts of interest of IRB members and make clear that any conflicted IRB member must be recused from any deliberations relating to studies with which that IRB member has a potential conflict of interest.*

B. Institutional Variations in Conflicts of Interest Policies and Practices

Under “Core Principles,” the 2001 AAMC Report states: “The Task Force recognizes that some institutions may determine that additional restrictions are appropriate. Likewise, we do not discourage institutional variations in process or in the allocation of the oversight responsibilities described in this guidance, provided that the review and management functions that we advocate are performed fully.”¹⁵

Recommendation: *While there are clear advantages to having somewhat uniform guidelines and policies for conflicts of interest in clinical research, universities and academic medical centers vary in many ways, including in their institutional cultures, traditions, missions and objectives, as well as in the populations they serve. The Advisory Committee thus endorses the statement on institutional variations in the 2001 Report, but strongly advises against variations that lead to standards less rigorous than those set forth in this Report.*

C. Conflicts of Interest in Clinical Practice

The Advisory Committee, while respectful of its circumscribed charge with respect to conflicts of interest in human subjects research, recognizes that many scientists who engage in human subjects research and have related significant financial interests also have active clinical practices in which those financial interests may be problematic and warrant institutional oversight. The Committee also recognizes that oversight and management of such conflicting financial interests of physician faculty in clinical practice settings is warranted.

Recommendation: *Institutions should adopt policies and establish standards that minimize bias in the practice of medicine due to real or perceived conflicts of interest of their medical faculty.*

¹⁵ Ibid. p.6.

D. Educating the Public, the Government, and the Media Regarding Avoidance and Management of Conflicts of Interest While Supporting Innovation in Clinical Research

Recommendation: *The Advisory Committee recognizes the benefit to the public, in general, and to the patient populations of our academic medical centers, in particular, of the translation of research into new therapies, devices, and disease-preventing strategies. The Committee also recognizes the substantial public benefits that would accrue from improving understanding of the ways in which research is funded, and of the extensive management procedures that are focused on potential conflicts of interest in human subjects research in order to avoid or limit any potential adverse effects from the conflicts.*

Therefore, the Committee strongly urges the AAMC, the AAU, and other professional organizations to take responsibility for developing and implementing strategies to educate the public, the media, and the government on the value of academic-industry relationships, and on how academic medical centers apply their conflicts of interest policies to protect the safety of human research subjects and the integrity of clinical research. Such educational strategies need to be implemented on a continuing basis over the long term and should not be confined to episodic responses to instances of public concern.

Chapter 2

Policies on Institutional Financial Conflicts of Interest in Human Subjects Research

A. Development and Adoption of Policies

Institutional conflicts of interest (Institutional COI), defined as conflicts of interest based on either the financial interests of the institution itself or of its officials acting in leadership or supervisory positions, are of special concern in the conduct of human subjects research. The perception that research involving human subjects—especially when there is greater than minimal risk for such individuals—might be motivated even in part by the possibility of personal or institutional financial gain cannot be tolerated. It is one of the core values of academic institutions that the protection of research subjects must not be compromised by the existence or even the reasonable appearance of institutional conflicts of interest.

Many institutions have developed policies and implemented procedures to eliminate or manage institutional conflicts and, at this writing, many others are working hard to develop and implement such policies. In support of this effort, the Advisory Committee here provides a reaffirmation, amplification, and refinement of the principles and frameworks already offered in the AAU and AAMC 2001 and 2002 guidance documents. Based on the experience of the intervening years, this Chapter discusses some of the especially difficult institutional COI issues that institutions must address, and offers a template for an institutional policy. The template is not offered as *the* model policy but rather as an example of how an institution might choose to address the topics identified in this chapter (Appendix A).

To the extent institutions have not yet done so, the Advisory Committee strongly encourages all institutions to develop their own institutional conflicts of interest policies consistent with these recommendations. The Advisory Committee believes that those institutions that are revising or amplifying their policies may find useful the tools offered here. Although the Advisory Committee was charged with examining institutional conflicts of interest specifically in the context of human subjects research, the Committee recommends that AAU and AAMC member institutions should commit themselves to develop and implement comprehensive institutional conflicts of interest policies that govern all operational aspects of a university or an academic medical center.

Recommendation: *The Advisory Committee recommends that all AAU institutions and AAMC schools of medicine and teaching hospitals should:*

- a. *develop an institutional COI policy covering both the financial interests of the institution and of institutional officials, including deans, department chairs and division chiefs, in human subjects research;*
- b. *implement an institutional COI reporting, evaluation, and management process, and create an objective and credible institutional COI review process involving a standing internal committee or an external review entity. Irrespective of their structures, these entities must be empowered to inform institutional leadership and decision-making;*

- c. complete policy development and implementation within two years of issuance of this report.

B. Definition of Institutional Conflict of Interest

There are two basic types of institutional conflicts of interest, one focusing on institutional transactions and holdings and the other on activities and holdings of institutional officials. This duality was well-defined in the 2002 AAMC Report, “Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of an Institution’s Financial Interests in Human Subjects Research”:

An institution may have a conflict of interest in human subjects research whenever the financial interests of the institution, or of an institutional official acting within his or her authority on behalf of the institution, might affect—or reasonably appear to affect—institutional processes for the conduct, review, or oversight of human subjects research.¹⁶

Understanding the full significance of this two pronged definition is very important. For individuals in high level positions of institutional responsibility, such as a dean, department chair, or division chief, a conflict between their personal financial interests and the institution’s human subjects research is more than an individual conflict; rather, it constitutes an institutional conflict of interest. The potential for institutional COI is especially acute in the case of department chair, division chiefs, and center and institute directors with financial conflicts of interest because they have direct oversight responsibility for individuals doing research related to the conflict.

C. Principles to Guide Management of Institutional COIs

1. Separation of Administrative Responsibility

Recommendation: *Research and financial decision-making processes and agents must be separated.*

If an institution fails to separate its responsibility for the oversight and administration of human subjects research from its responsibility for the management of the institution’s financial interests, the risks of compromising the safety of human subjects and the integrity of the research performed are significantly heightened. Institutions and institutional officials must segregate individuals who are entrusted with making decisions about research policy from all decisions, processes, and projects involving institutional business investments or other financial interests. Most institutions of higher education have established firewalls for these purposes. However, at some high level, the two streams of finance and research oversight inevitably converge. Therefore, systems should be in place, either in the office of

¹⁶ AAMC Task Force on Financial Conflicts of Interest in Clinical Research: *Protecting Subjects, Preserving Trust, Promoting Progress II—Principles and Recommendations for Oversight of an Institution’s Financial Interests in Human Subjects Research*, p.2.

the university chancellor or president, or other high ranking university official, to ensure that human subjects safety and the integrity of the data generated in human subjects research remain the institution's top priority. Even where the separation of function is secured by a strong firewall, certain financial relationships with commercial research sponsors should be examined closely to avoid institutional conflicts of interest.

2. Rebuttable Presumption

Recommendation: *Decisions about whether or not to pursue a particular human subjects research project in the presence of an institutional conflict of interest should be governed by a “rebuttable presumption” against doing the research at or under the auspices of the conflicted institution.*

As defined in AAMC's 2002 Report:

The presumption may be rebutted when the circumstances are compelling and the committee has approved an effective conflict management plan. Whether the [institutional conflicts of interest] committee deems the circumstances to be compelling should depend in each case upon the nature of the science, the nature of the interest, how closely the interest is related to the research, the degree of risk that the research poses to human subjects, and the degree to which the interest may be affected by the research. The committee should consider whether the institution is uniquely qualified, by virtue of its attributes (e.g., special facilities or equipment, unique patient population) and the experience and expertise of its investigators, to conduct the research and safeguard the welfare of the human subjects involved. Even when the institution is deemed uniquely qualified, conflicts associated with significant risk to human subjects should be avoided whenever possible and, if permitted, should be managed closely.¹⁷

While there may be “compelling” circumstances under which this presumption can be overcome, the decision to allow the research to proceed should be made through a rigorous, codified and transparent institutional COI evaluation process.

3. Consistent Implementation

The evaluation of whether or not compelling circumstances exist should initially be the responsibility of a standing Committee, with ultimate authority for decision making vested in the president/chancellor or governing board, as institutional governance provides. If the institutional COI Committee determines that the project should be allowed to proceed, it should approve and document the bases and conditions for its decisions, as provided below. If human subjects are involved, the institutional COI Committee report should be provided to the relevant IRB. Under certain circumstances, external IRB review and external monitoring as well as other tools for managing institutional COI may be considered to ensure that the research is adequately monitored. The IRB should require disclosure of institutional COIs in informed consent documents and in other relevant contexts.

¹⁷ Ibid. pp. 10-11.

Recommendation: *Institutions should assure in policy and practice that institutional COIs will be addressed consistently throughout the institution, such that those subject to institutional financial conflict of interest policies, specifically officials of the institution and the institutions themselves, are subject to substantive reporting, disclosure, and management of their financial interests to protect the integrity of human subjects research and the subjects who participate in it, as well as institutional values and decision-making.*

D. Key Institutional COI Policy Provisions and Processes

As part of defining its approach to institutional COI, each institution's policy should:

1. Determine whether potential conflicts of interest of institutional officials, board members, and officials, including deans, department chairs, division chiefs, and center and institute directors, overseeing human subjects research should be addressed through the institution's institutional COI policy or its policy on individual conflicts of interest.
2. Determine who the covered institutional officials are. This determination could be by title (e.g., Chancellor, President, Dean, Department Chair, Center or Institute Director, Division Chief, etc.), or by function (i.e., involvement in elements of oversight or decision-making regarding human subjects research), or by both. Institutions should take care to define how inclusive this designation is to be.
3. Define institution-specific (*de minimis* or *other*) reporting standards for institutional holdings. In the case of institutional officials, specify which of their activities and assets are covered by the institution's individual conflicts of interest policy, and which fall under the institutional conflicts of interest policy.

In addition, institutions should adopt the following processes:

4. All financial interests of the institution and of institutional officials should be reported to a designated institutional office (and updated regularly), and should be reviewed in accordance with the institutional COI policy.
5. An institutional COI Committee should be established, as is more fully described in Section 7. Note that an institution may choose to use the committee that it established to address individual conflicts of interest.
6. The institutional office in charge of technology transfer and licensing should report to the institutional COI Committee (or a designated institutional official) whenever, as a result of a licensing agreement, the institution takes (or intends to take) equity, royalty, or other stake in a sponsor of human subjects research, and whenever, as part of the agreement, the company is permitted to participate in human subjects research at the institution.

7. An institutional reporting link should be established between the institutional COI process and the IRB.
8. When the institutional COI Committee determines whether a potential institutional COI should be eliminated or whether it can be managed to allow the research to go forward, such decisions should be documented and communicated to affected individuals and officials.
9. Gifts to the University must be differentiated from sponsored research agreements and grants. A gift should not be burdened with any explicit or implicit conditions regarding quid pro quo, while a grant may contain conditions regarding the sharing of information in a manner consistent with the university's mission, research policies, and non-profit status. Both have the potential to create institutional COI and may need to be considered by the institutional COI Committee, as provided below.
10. Because gifts and philanthropy can create potential institutional COI, institutions should authorize only designated institutional officials to receive gifts, monetary or otherwise, on behalf of the institution.
11. Institutional COI policies should be publicized on campus and made available to the public.

E. Identification of Potential Institutional COIs

Given the two pronged definition of institutional COI, two institutional processes are essential to identify potential conflicts. First, systems should be in place to report to the designated office or official when relationships develop between the institution and entities that sponsor research or between entities whose product is being studied in research at the institution. Secondly, systems should be in place to determine when individuals in a decision-making capacity have financial relationships that might be perceived to affect their judgment or choices.

One or more of the following circumstances may create potential institutional COI in human subjects research. Accordingly, if any one of these exists, the institution should conduct a specific, fact-driven inquiry into whether the particular financial relationship may affect or reasonably appear to affect human subjects research conducted at or under the auspices of the institution:

1. When the institution is entitled to receive royalties from the sale of the investigational product that is the subject of the research;
2. When, through its technology licensing activities or investments related to such activities, the institution has obtained an equity interest or an entitlement to equity of any value (including options or warrants) in a *non-publicly traded* sponsor of human subjects research at the institution;

3. When, through technology licensing activities or investments related to such activities, the institution has obtained an ownership interest or an entitlement to equity (including options or warrants) of greater than \$100,000 in value (when valued in reference to current public prices, or, where applicable, using accepted valuation methods), in a *publicly-traded* sponsor of human subjects research at the institution; or
4. When, with regard to a specific research project to be conducted at or under the auspices of the institution, institutional officials with direct responsibility for human subjects research hold a significant financial interest in the commercial research sponsor or the investigational product. “Significant financial interest” is defined for this purpose as being consistent with the institution’s individual conflict of interest policy. In AAMC’s 2002 guidelines for institutional COI, the definition includes the following:
 - a. An equity interest or entitlement to equity (including options or warrants) of any amount in a *non-publicly traded* company that is i) the sponsor of human subjects research at the institution, or ii) the manufacturer of a product to be studied or tested in human subjects research at or under the auspices of the institution;
 - b. An equity interest or entitlement to equity (including options or warrants) in excess of the *de minimis* amount (and not including exceptions for certain mutual funds), as defined in the AAMC’s 2001 guidelines for individual financial interests, in a publicly traded sponsor of human subjects research conducted at or under the auspices of the institution;
 - c. Consulting fees, advisory board fees, remuneration, honoraria, gifts or other emoluments, or “in kind” compensation from a company that is i) the sponsor of human subjects research at the institution or ii) the manufacturer of a product to be studied or tested in human subjects research at or under the auspices of the institution, that in the aggregate exceed the *de minimis* amount as defined in the AAMC’s 2001 guidelines for individual financial interests, or are expected to exceed that amount in the next 12 months;
 - d. An appointment to serve, in either a personal or representative capacity, in a fiduciary role for a company that is i) the sponsor of human subjects research at the institution or ii) the manufacturer of a product to be studied or tested in human subjects research at or under the auspices of the institution, whether or not remuneration is received for such service. Typically, the appointment will involve service as an officer, director, or other board member of the company.

- e. An appointment to serve on the scientific advisory board of a commercial sponsor of human subjects research conducted at or under the auspices of the institution, unless the official has no current significant financial interest in the sponsor or the investigational product and agrees not to hold such an interest for a period of no less than three years following completion of any related research conducted at or under the auspices of the institution.

In addition, there are other relationships that may warrant special scrutiny. Institutions should determine the nature and degree of scrutiny required for any of these relationships or interests by assessing the potential of institutional COI and weighing the magnitude of any risk to human subjects. Such relationships include but are not limited to the following:

1. When an investigator, research administrator, or institutional official with research oversight authority participates materially in a procurement or purchasing decision involving major purchases from, or non-routine supply contracts with, a commercial entity that sponsors human subjects research at the institution; or
2. When the institution has received substantial gifts (including gifts in kind) from a potential commercial sponsor of human subjects research. Evaluation of the potential sponsor's gift history might include the following:
 - a. Whether a gift is of sufficient magnitude that even when held in the general endowment for the benefit of the entire institution, it might affect, or reasonably appear to affect, oversight of human subjects research at the institution;
 - b. Whether a gift is held for the express benefit of the college, school, department, institute or other unit where the human subjects research is to be conducted; or
 - c. Whether any institutional officer who has the authority, by virtue of his or her position, to affect or appear to affect the conduct, review or oversight of the proposed human subjects research has been involved in the solicitation of the gift.

F. Analysis of Potential Institutional COIs

Once a potential institutional COI is identified, a determination must be made whether or not compelling circumstances justify overriding the rebuttable presumption against conducting the research. The resolution of that question should take into account and document in a report the following:

1. The nature of the science involved;
2. A description of the institutional COI and how closely it is linked to the research;
3. The magnitude of the potential risks to research subjects inherent in the research, and how those risks could be affected as a result of the institutional COI;

4. The degree to which the involved parties stand to benefit from the research;
5. A decision of whether or not compelling circumstances exist to allow the research and if so, the reason for the determination;
6. If compelling circumstances exist, a specification of the elements of the management plan that includes:
 - a. Notification of the IRB (for consideration of the risk-benefit ratios and inclusion of disclosing language in the informed consent process/document, among other things);
 - b. Notification of the sponsored programs office to alert sponsoring entities and to comply with applicable federal requirements if federal funding is involved;
 - c. Requirements regarding disclosure of the institutional COI in publications, presentations, future grant applications, and other types of communication.

This report should be reviewed and approved by the institutional COI Committee, as provided in Section 7.

G. Institutional COI Committee

Recommendation: *Institutions should form a standing institutional COI Committee to review and analyze potential institutional COIs, as defined above. [Note that institutions may choose to use for this purpose the committee established to address individual COI.] The Committee must be able to analyze when it would be appropriate and in the public interest to accept and manage a conflict, rather than require that it be eliminated.*

1. The Committee should be empowered to address situations where external financial relationships and research interests overlap, including real and potential institutional COI (unless the institutional COI has already been addressed by recusal or elimination).
2. If the Committee determines that recusal would not be an effective management strategy because the individual would be precluded from fulfilling the responsibilities of his or her position, the interests of the institution may necessitate that the individual officer eliminate the holdings or vacate the institutional position.
3. The Committee should be comprised of individuals with sufficient independence, expertise, and seniority.
4. The Committee, to the maximum extent possible, should be independent of the line of authority for institutional oversight of human subjects research. Wherever possible, the inclusion on the Committee of one or more external ('public') members is strongly recommended. Public representation assures that at least one committee member is free of institutional conflicts and

perceived to be independent of the institution, and it may serve to enhance the credibility of the process with the public. However, for some institutions, public members may not be feasible because of particular governance or policy constraints.

In most cases, the institutional COI Committee should make recommendations to an official with operating authority over the situation who has direct access or reports to the University President/Chancellor or Board of Trustees, as institutional governance provisions specify. The Committee should have the authority to make significant recommendations including:

1. Prohibiting the proposed research at the institution or justifying the decision to allow certain projects to proceed under managed conditions;
2. Eliminating, reducing, or modifying the institution's financial stake;
3. Increasing or establishing firewalls or other conflicts management systems to separate financial and research decision-making;
4. Setting up a credible monitoring process to enable close scrutiny of the research to protect its integrity and the well-being of human subjects.

In the case of institutional officials, many recommendations for safeguarding against institutional COI are described in Chapter 3 of this report, in the Section on Management Strategies. Institutions may also consider using the following:

1. Isolating/recusing the conflicted official(s) from involvement in the research or decision-making regarding the research;
2. Recommending that the conflicted official(s) reduce, modify, or eliminate their equity holdings or royalty income.

H. Policy Adoption and Implementation

The development and implementation of institutional COI policies has proved to be challenging for many institutions.¹⁸ Some institutions have struggled with drafting institutional COI policies, some have faced difficulties in implementing institutional COI policies, especially because of the need to create new, coordinated, institutional information systems, and others have found challenges in managing identified institutional COIs. The Advisory Committee intends that the discussion of institutional COI policy principles and processes in this chapter, the template institutional COI policy in Appendix A and the case study materials in Appendix B will be helpful to institutions and will enable them more comprehensively, effectively, and expeditiously to address the many challenges associated with institutional COI.

¹⁸ Ehringhaus SH, Weissman JS, Sears JL, et al. Responses of Medical Schools to Institutional Conflicts of Interest. *JAMA*.2008;299(6):665-671.

Chapter 3

Implementation of Conflicts of Interest Policies

A. Introduction

The absence of specific guidance on implementation of the 2001 and 2002 AAU and AAMC guidelines has contributed to inconsistency in implementation practices across institutions. Some inconsistencies result from legitimate institutional differences and different regulatory frameworks facing these institutions. Federal regulations themselves endorse institution-specific approaches to conflicts of interest policies and practices, within the established regulatory framework. However, many differences may result simply from the lack of widely accepted templates for approaching conflict of interest evaluation and management. Still other problems may result from insufficient attention to ensure that established policies and procedures actually work as intended and are consistently applied and enforced.

This section of the report addresses possible inconsistencies and problems in implementation and offers guidance under the following headings: Analysis of Cases Involving Potential Conflicts of Interest in Human Subjects Research, Management of Conflicts of Interest, Monitoring Conflicts Programs, and Management of Conflicts of Interest, External Professional Activities and Consulting, and Education.

B. Analysis of Cases Involving Potential Conflicts of Interest in Human Subjects Research

Both the AAU and the AAMC guidelines recommend that institutions establish a Conflict of Interest (COI) Committee to evaluate instances of potential conflicts of interest in research and to propose to the institution appropriate strategies for addressing such conflicts. Additional guidance is offered here on how instances of potential conflicts of interest might be addressed by the Committee, with respect to the values that the conflicts of interest process should preserve and in terms of the actual process for analysis and resolution.

1. Responsibilities of Conflict of Interest Committees

When analyzing cases that are brought before it, a COI Committee should keep in mind certain responsibilities and should adopt a consistent approach to examining cases. The responsibilities include, at a minimum:

- a. Protecting the safety of human subjects who participate in research;
- b. Protecting the integrity of data and information generated by the researchers in their research and provided to the public, trainees, and peers;
- c. Safeguarding the reputations of the researchers and the institution as both carry out their activities related to the research;
- d. Protecting core academic freedoms and in particular, the right of faculty to publish the results of their scholarship, the integrity of the educational process, and the free academic exchange of trainees engaged in research; and

- e. With the institutional administration, educating and assisting the covered faculty and research staff in the ethical and responsible conduct of research.

2. Framework for Analysis

The analysis template found in Appendix B provides a framework by which a COI Committee should evaluate facts that present potential conflicts. The cases in Appendix B provide examples of typically recurring conflicts and illustrate the application of the analysis template to particular facts.

C. Management of Conflicts of Interest

The 2001 AAMC Report states that “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.”¹⁹ This section offers guidance on the formulation of management plans.

As indicated previously, research involving human subjects conducted in academic institutions should reflect three fundamental values: protection of the research subjects, upholding the integrity of the research, and maintenance of public trust in the independence of the academic institution and its personnel. Where potential conflicts of interest are present, decisions regarding management of those conflicts should be conditioned on assuring that the fundamental purposes of clinical research are served.

1. Compelling Circumstances and Risk Benefit Analysis

The principles by which institutions should approach conflicts of interest in clinical research were articulated in the 2001 AAMC Report as follows:

“With the welfare of research subjects always of foremost concern, an institution should regard all significant financial interests in human subjects research as potentially problematic and, therefore, as requiring close scrutiny. Institutional policies should establish the rebuttable presumption that an individual who holds a significant financial interest in research involving human subjects may not conduct such research. The intent is not to suggest that every financial interest jeopardizes the welfare of human subjects or the integrity of research, but rather *to ensure that institutions systematically review any financial interest that might give rise to the perception of a conflict of interest, and further, that they limit the conduct of human subjects research by financially interested individuals to those situations in which the circumstances are compelling.* The presumption against significant financial interests in human subjects research should apply whether the research is funded by a public agency, a non-profit entity, or a commercial sponsor, and wherever the research may be carried out.”²⁰

¹⁹ Ibid. p.15.

²⁰ Ibid. p.7, emphasis added.

“In the event of compelling circumstances, an individual holding significant financial interests in human subjects research may be permitted to conduct the research. Whether the circumstances are deemed compelling will depend in each case upon the nature of the science, the nature of the interest, how closely the interest is related to the research, and the degree to which the interest may be affected by the research...”²¹

“When an institution finds that financial interests in human subjects research are justified by compelling circumstances, those interests and the research in question must be managed through *rigorous, effective, and disinterested monitoring* undertaken by individuals with no financial or professional ties to the research or direct reporting relationships to the researchers.”²²

The process by which an institution determines whether a particular researcher with a related financial interest will be permitted to participate in a human subjects research project begins with the individual’s reporting of his or her financial interests to the institution. At that point, the institution must evaluate the financial interests, their relation to the proposed research, and the individual’s relation to the research. This examination leads to the decision whether the individual may be permitted to participate in the proposed research, with or without elimination, reduction, or management of the identified conflict.

The outcome is dependent on a determination of whether or not compelling circumstances exist and if they do, on a risk-benefit analysis that balances the potential benefits of the project and the individual’s participation in it with the risks to subjects, risks to integrity of research data, risks of bias, and risks of the appearance of conflict. The rebuttable presumption/compelling circumstances standard is intended to be a high bar, not readily overcome. The rebuttable presumption is that the conflicted individual is prohibited from participating in human subjects research. Only when circumstances are compelling should the presumption be rebutted and “rigorous, effective, and disinterested monitoring” be undertaken.

²¹ Ibid.

²² Ibid. p. 9.

The robustness of any risk-benefit analysis is dependent on an awareness of the available techniques for management of the conflict and on the careful, case-specific assessment of their effectiveness under the particular circumstances of the proposed research. To assist in identifying and evaluating the potential effectiveness of available management techniques, it may be useful to consider the following questions:

- Are basic academic values upheld?
- Is an open academic environment maintained?
- Do the conflicted investigator and institutional resources bring unique capabilities to the research?
- Is the research appropriate to the mission of the institution?
- Are there restrictions on publications or dissemination of research results?
- Are uses of institutional resources and facilities appropriate?
- How great is the risk to human subjects?
- Are the roles of students, trainees, and junior faculty and staff appropriate and free from exploitation?
- Are there appropriate channels for communication and oversight of the research project?
- Are significant benefits to society likely to result from advancing the research?

2. Selection of Strategies for Managing Conflicts of Interest in Clinical Research

Strategies for management of potential conflicts of interest range from highly specific conditions for researcher participation in the research project to more abstract assurances of compliance, but all are directed at ensuring integrity, protection of subjects, and public trust. The examples provided in this section do not represent a complete list of all management techniques and strategies, but rather a collection of approaches that academic institutions have used to mitigate the challenges posed by potential conflicts. They are intended to provide a range of options from which institutions might choose, depending on the circumstances of a particular case. There is no formula that dictates which strategies “fit” which conflicts. The final determination is dependent on an individualized assessment at the local institutional level of the totality of the circumstances that need to be taken into account. Each institution is best positioned to make this assessment on its own behalf, consistent with the framework for federal regulation of conflicts of interest and with the institution’s responsibility for the quality and integrity of the research conducted under its auspices.

A key component of any management strategy is the understanding by the conflicted individual that management is a process that begins with the approval of a management plan and requires the individual’s active participation, commitment and vigilance throughout the duration of the plan. Institutions should carefully attend to this aspect of education on conflicts of interest.

3. Management Plans

The examples of conflict management techniques provided here are grouped under general topic headings for ease of reference. Whatever techniques are selected by the institution, it is essential to the credibility of its conflict of interest program that the development of the management plan constructively engage the conflicted researcher, and the agreed-upon provisions to manage conflicts should be recorded in the management plan. These plans provide a record of deliberations and decisions, and a reminder to affected parties of their responsibilities, institutional precedent, and evidence of accountability.

a. Management Techniques—Disclosure

Disclosure relates to the release of relevant information about financial interests in particular human subjects research to parties within and outside the institution. Though disclosure alone would very rarely be considered adequate to manage an identified conflict, it is an essential initial step. There is general agreement that the disclosure must be sufficiently detailed to enable those to whom disclosure is made to understand key elements of the conflict. Usually, disclosure of a conflict is predicated on a notion that the disclosure empowers the recipient by enabling that person to account for the conflict in his or her evaluation of the research. However, this notion presumes, often unrealistically, that those to whom disclosure is made have the knowledge and capacity necessary to make such adjustments. On the other hand, not to disclose identified conflicts to affected groups is a violation of accepted academic standards and exposes the conflicted individual and the academic institution to charges of secrecy, misrepresentation, and deception.

With respect to any given research project, disclosure is limited to those financial interests that relate to that research project itself. As stated previously, the document or statement by which disclosure is made need not itself contain all the relevant information, on the condition that the disclosure includes a clear reference to the presence of the conflicting interest, and an indication that additional information is available upon request regarding the details of the conflicting interest, how it is being managed, and how it can be readily obtained by those to whom the disclosure is made. Those groups of individuals to whom disclosure generally should be made, or contexts in which it should be made, include, but may not be limited to, the following:

1. In IRB-approved consent forms, with an explanation that additional information will be provided to the research subjects upon request. It should be recognized that notification of research subjects falls within the purview of the applicable IRB, which determines whether and how the conflict of interest should be disclosed to the relevant human subjects.
2. To the editors of any publication to which a conflicted individual submits a manuscript reporting the research, and to the conveners of conferences and meetings to which a conflicted individual submits an abstract of a presentation for dissemination to the audience;

3. In any substantive oral or written public communication of the research results, including not only to the research community but also to lay audiences and the press;
4. To research funders and sponsors;
5. To federal and/or state officials as required by federal and/or state law or regulation;
6. To all of the researchers, research personnel, students, and trainees working on the research project (and, where circumstances warrant, to their supervisors);
7. To the conflicted individual's immediate supervisor (e.g., chair, division director, dean, etc.);
8. To the sponsor of multi-center trials and to IRBs of the other participating institutions;
9. When relevant, to clinic or hospital administration.

Institutions should consider periodic self-certification by conflicted individuals as a means of reminding individuals of their responsibilities to comply with all elements of their agreed management plans and to record individuals' understanding and commitment. This technique is discussed in more detail in the Section entitled "Monitoring Conflicts Programs and Management of Conflicts of Interest."

b. Management Techniques—Human Subjects

It is critically important for institutions to develop specific policies for protection of human subjects in the presence of conflicts of interest. When the COI Committee devises any conflicts management plan, special attention must be paid to focusing its strategies on the protection of subjects. Interactions between a conflicted researcher and the subjects participating in the proposed research must receive the strictest scrutiny because the interactions are fraught with ethical dilemmas and carry potential for harm. The restriction of a conflicted investigator's role in the research project, adjusted to the level of anticipated risk, is the principal strategy for protection of subjects. Accordingly, the following questions should be addressed by the COI Committee in determining what role, if any, a conflicted investigator should play in interacting with subjects.

1. Under what circumstances, if any, should a conflicted individual be allowed to participate in subject recruitment?
2. Under what circumstances, if any, should a conflicted individual be allowed to participate in subject selection, including prescreening for inclusion/exclusion criteria?
3. Under what circumstances, if any, should a conflicted individual be allowed to participate in the consent process?

4. Under what circumstances, if any, should a conflicted individual be allowed to participate in clinical treatment of subjects, separate from the research interventions or procedures?
5. Under what circumstances, if any, should a conflicted individual be allowed to participate in clinical evaluation of subjects during the research, separate from the research interventions or procedures, including adverse event evaluation and reporting?

c. Management Techniques—Students and Trainees and Colleagues

The involvement of students and trainees in research projects is vital to their educational experience, and they are also key contributors to the knowledge creation enterprise. As they are being prepared for their professional careers, students and trainees should be provided with opportunities to learn about interactions with industry and about risks to human subjects and research integrity in the presence of conflicts of interest. When students, trainees and/or their junior colleagues participate in human subjects research projects with a conflicted faculty member, there is serious potential for real or apparent coercion, for differential inclusion and exclusion of individuals, and for interference with academic programs and progress. For these reasons, institutional policies should require special provisions for the protection of vulnerable members of the research team. Institutions should address the following issues:

1. Under what circumstances, if any, should students, trainees, and/or junior faculty and staff be allowed to participate in research projects conducted by conflicted senior or supervising faculty and staff?
2. Under what circumstances, if any, should students, trainees, and/or junior faculty and staff be allowed to work in newly-formed companies involving conflicted faculty and staff who have supervisory or other positions of authority or influence over the students, trainees, or junior faculty and staff?
3. Under what circumstances, if any, should students, trainees, and/or junior faculty and staff working on the project be informed of the potential conflict?
4. Under what circumstances, if any, should academic decisions outside the research activity by conflicted individuals that involve students, trainees, and/or junior faculty and staff working on the project be reviewed by others?
5. Under what circumstances, if any, should students, trainees, and/or junior faculty and staff working on the project be provided with access to senior faculty and staff or administrators who are not involved with the research project to ensure independent review of any questions or concerns they have about the research?

d. Management Techniques—Research and Data Integrity

No single strategy can insure integrity of the research or of the underlying data under all conditions, but where risks to human subjects research and data integrity are identified, consideration should be given to the use of one or more of the following techniques:

1. Independent data monitoring to ensure validity, through an objective individual or individuals in the institution with no ties to the research or to the outside entity. Institutions should also consider the additional value of engaging individuals from outside the affected institution. Engaging outsiders is particularly useful when the institution itself is also perceived to have a conflict in the research, or where the risks to data integrity are particularly high. Data monitoring can be accomplished by a standing committee, but may be more effective if individuals with familiarity and expertise in the area of the research are engaged on a case-by-case basis. Institutions should be aware, however, that individuals or committees engaged to perform this task may require compensation, and the institution should be prepared to decide how these costs are allocated. Further, the institution should give careful attention to the assignment of responsibility for arranging such duties and for oversight during the performance of these duties.
2. Review of the study design to address potential bias arising from the financial interest;
3. Prohibition of involvement of a conflicted individual as principal investigator;
4. Prohibition of involvement of a conflicted individual as co-PI or investigator;
5. Prohibition of involvement of a conflicted individual in data collection;
6. Prohibition of involvement of a conflicted individual in data analysis;
7. Review of authorship status;
8. Oversight of the entire research project by an individual or a group of individuals with sufficient independence and expertise to evaluate the research and the progress of the project. The individual(s) may be from within or outside the institution.

e. Management Techniques—Financial Interests

Various forms of managing the financial interests themselves may also be considered as strategies for eliminating, reducing, or managing identified conflicts in human subjects research. These strategies focus on the nature of the financial interest and/or on the relation of the conflicted individual to the outside entity that is the source of the financial interest. They involve restrictions on the financial interests themselves, rather than on activities of the researcher. A COI Committee may consider the following actions:

1. Divestiture of the respective interest(s);
2. Reduction of the amount of the interest to an acceptable level, if one exists;
3. Restriction in exercising/trading stock options or stock. However, caution should be exercised in devising such restrictions as management strategies because of the appearance of potential manipulation of share price;
4. If the interest consists of royalty payments, research-related milestone payments, or related payments received in partial or full compensation for licensing of the technology that is the subject of research, the institution may wish to consider deferral or waiver of payments. The boundaries could be set by specified timelines and/or the elimination of payments that are triggered by research milestones.

f. Special Considerations for Start-Up Companies and Small Ventures

In the context of human subjects research, considerable risks are associated with the participation by a conflicted individual in activities of an outside entity that is the source of the conflict with the particular research project, especially a new or a small venture. These risks are high in terms of potential distortion of primary commitments to the institution, to students and trainees, to faculty and staff, and to the institutionally-based research project. How institutions address these risks must be closely linked to an assessment of the particular facts and circumstances of specific situations and to their institutional consulting and conflicts of commitment policies. However, conflicts of interest are also common in such situations. Accordingly, to address the role of the individual in the outside entity when the individual is performing research related to the entity, a COI Committee should consider placing the following restrictions on the conflicted individual:

1. Prohibition of participating in institutional negotiations with the company, except as the institution directs;
2. Prohibition of serving on board of directors;
3. Prohibition of serving as an officer;
4. Prohibition of serving as a member of the scientific advisory board;
5. Prohibition of serving as a member of a speakers' bureau;
6. Prohibition of serving as a consultant;

7. Prohibition of disclosure of institutional confidential information; prohibition of channeling discoveries to the outside entity;
8. Prohibition of receiving research grant support from companies founded by the conflicted individual.

g. Special Considerations for Conflicted Administrators and Supervisors

The AAMC's 2002 Guidance on Institutional Financial Conflicts of Interest in Human Subjects Research notes that "... an official's position may convey an authority that is so pervasive or a responsibility for research programs or administration that is so direct that a conflict between the individual's financial interests and the institution's human subjects research should . . . be considered an 'institutional conflict of interest.'"²³ But in addition to whether and how, if at all, such conflicts should be managed by and for individuals, another value is at stake in addition to those previously identified. "Beyond compliance with policies and procedures, institutional officials must foster what has been described as a 'culture of conscience' in the research enterprise. . . . Leading by personal example, officers and administrators should demonstrate to the academic community and to the public that responsible, accountable, and ethical behavior regarding financial conflicts of interest is an imperative, reflecting core institutional values."²⁴

Because financial conflicts of administrators can have an adverse impact on this "culture of conscience," special attention must be paid to the selection of management strategies for conflicted individuals who occupy administrative or oversight roles. Individuals with such responsibilities include institutional board members, presidents and chancellors, vice presidents or provosts for research, deans and associate deans, department chairs, and division chiefs. In addition, in academic institutions some *de facto* supervisory roles may exist, as a consequence of influence, funding, seniority, or other factors. Accordingly, careful attention should be paid to the personal circumstances of a conflicted individual as well as to any official administrative positions that a conflicted individual may hold.

Four options in addition to those already discussed, may be useful for a COI Committee to consider in the case of conflicted individuals who have administrative or supervisory roles:

1. Recusal of the conflicted administrator from institutional decisions related to the outside entity that is the source of the financial conflict;
2. Periodic written disclosure of the conflict by the conflicted individual to all faculty, staff, and students under his or her supervision;
3. Research oversight committees;

²³ AAMC, Task Force on Financial Conflicts of Interest in Clinical Research: *Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research*, (October 2002), p.4.

²⁴ Ibid. p.5

4. Appointment of independent, disinterested individuals or committees to oversee leadership or high-level administrative decisions (financial decisions, space allocations, appointments and promotions, and the like) to prevent preferential treatment or misdirected resources.

D. Monitoring Conflicts Programs and Management of Conflicts of Interest

As provided in the AAMC 2001 Report, “Institutions should regularly assess compliance with COI policies through the use of internal audit mechanisms and other appropriate self-evaluation strategies.”²⁵ This section provides guidance on implementation of that recommendation.

1. Accountability

Institutions have a responsibility to assure themselves that their conflict of interest policies and procedures are working effectively. Beyond that, there is renewed congressional interest and pressure on NIH to ensure that institutions are diligently enforcing their conflict of interest policies and adhering to federal regulations. The ways institutions select to do so should reflect institutional culture, accommodate administrative and fiscal circumstances, and provide necessary documentation of compliance with applicable federal and state requirements on conflicts of interest in research. Beyond legal requirements, however, this oversight activity is an integral aspect of assuring data integrity, subject protection, and public trust.

a. Oversight

In addition to assuring that policy provisions are followed, a key emphasis of any oversight program should be on compliance with the conflict management plans, and on education of faculty and staff to ensure that management is an ongoing participatory process requiring their active attention. Thus, initial management plans may be augmented with provisions for additional oversight to enable the institution to ascertain that its decisions have been implemented and its policies enforced. This oversight function has the potential of shifting the emphasis of conflicts management from being based on integrity and trust towards one focused more on mandated compliance. It is important therefore to create a balance between the two, to reflect not only fundamental institutional values but also to incorporate institutional and individual accountability and responsibility. These are key elements in the success of a conflicts of interest program. Individual accountability should be reinforced by including in conflicts of interest policies the notion that failure by a conflicted individual to comply with provisions of management plans is subject to the full range of institutional disciplinary procedures as provided in applicable disciplinary policies.

²⁵ AAMC, Task Force on Financial Conflicts of Interest in Clinical Research: *Protecting Subjects, Preserving Trust, Promoting Progress—Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research*, (December 2001) p.21.

b. Institutional Databases

Regardless of institutional differences, the establishment of an institutional database is essential. It is the prerequisite for being able to identify institutional COI, for establishing optimally effective education and oversight systems, and for demonstrating accountability. In addition to allowing identification of institutional COI, such systems facilitate overview of all requisite aspects of case management, and establish communication among key players in the management process. It is most desirable that such databases should be sufficiently comprehensive to integrate the unit that oversees education on the ethical conduct of research, the IRB, the technology transfer office, the sponsored programs office, the office that handles gifts to the institution, and the conflicts of interest and commitment office. Comprehensive systems of this kind would not only assist institutions in dealing with the complexity of the large universe of parallel clinical research activities, but also allow them to extract specific data sets to measure the effectiveness of case management and of oversight systems.

2. Monitoring

Institutions should consider certification by conflicted individuals to the COI Committee or others that they are adhering to their management plans. Such a process of self-certification may be a useful in strategies for managing conflicts of interest. It would serve as a reminder to the conflicted individual of their compliance responsibilities, and it would serve the institution as documentation of individual cooperation with various management provisions. Central collection of the multitude of separate data that are integral parts of each approved management plan can represent a major undertaking for COI Committees, resulting in significant logistical and cost implications. Self assurances on the other hand, might free those charged with the management of conflicts from some of the responsibility for independently documenting compliance with various provisions. Self certification initiatives should be subject to periodic audits to demonstrate that they are functioning appropriately.

Institutional monitoring represents an alternative to a self-certification system with periodic auditing. The extent of monitoring will depend on the particular institutional policies but especially on the facts and circumstances of individual cases and any special sensitivities associated with them. However, the following are areas, systems, tasks, and activities that generally may be considered relevant for monitoring. Attention should always be given, in each area monitored, to the frequency, the scope, the methods, and the results of the monitoring.

Consideration must also be given to how the reports of results will be used and to the potential consequences of the results.

Institutions should consider selecting one or some of the items among those listed below rather than including all items in prospective monitoring plans.

1. Evidence that management plans have been followed (the management plans themselves may be used as a checklist):
 - a. Copies of items that the conflicted individual agreed to supply;
 - b. Copies of reports of any oversight individual or group;
 - c. Copies of data analysis plans;
 - d. Copies of assurances;
 - e. Copies of disclosures;
 - f. Copies of publications;
 - g. Copies of communications with trainees about the conflict;
 - h. Review of posters, abstracts, data, and other materials;
 - i. Review of financial records associated with the financial interest.
2. Evidence that the institution's conflict policies and procedures are followed:
 - a. Records of reports of financial interests by individuals subject to the conflict of interest policy;
 - b. Records of consulting and other external relationships;
 - c. Records of gifts to the institution;
 - d. Schedule of regular meetings of the conflict of interest review committee(s);
 - e. Minutes from such meetings;
 - f. Records of disclosures of potential conflicts of interest to various groups or individuals;
 - g. Minutes and records of oversight groups or arrangements;
 - h. Records of conflict management plans;
 - i. Records of notifications to NIH.

E. External Professional Activities and Consulting

Policies and practices regarding external professional activities or consulting vary widely from institution to institution, even though most policies are built upon similar assumptions. The assumptions include the primacy of the faculty and staff members' obligations to the academic institution and the necessity to restrict external commitments that compromise primary obligations. Institutional differences relate to whether or how much effort employees may devote to professional activities or to consulting outside the institution. Universities also vary regarding their level of awareness of and involvement in external activities of their employees.

Consulting is often a highly visible external activity in which faculty and staff participate, and consulting relationships frequently create potential conflicts in human subjects research, regardless of the particulars of the applicable institutional policy. Accordingly, it may be useful to examine possible areas of institutional involvement in faculty consulting as a means to evaluate local policies. Examples of such areas are provided in Appendix D.

The levels of involvement by the institution can range from minimal reporting requirements to the necessity for prior review and approval of proposed activity. Some institutions decline to review contractual arrangements in order to avoid any implication of institutional sponsorship or endorsement, while others require full institutional contract review and approval. State or system wide regulations also may have an impact on institutional consulting policies.

F. Education

Adequate education of faculty and staff on an institution's conflict of interest policies and procedures is essential to any responsible conflict of interest program. Various institutions have developed institution-specific educational materials. The willingness of those institutions to share such materials nationally could provide a means to assist other institutions in the performance of this responsibility. Because it is vital that constructive relationships between academe and industry persist and flourish, it is inevitable that students and trainees will be exposed to such relationships, if not in the educational setting, certainly once their training is complete. Therefore, it is important that they be exposed during their training to how to respond to those forces that may challenge objectivity and independence. The topic of conflicts of interest should be incorporated into appropriate curricular offerings for students and trainees. For the research community in general, training in conflicts of interest is imperative. The Advisory Committee commends Appendix B as a means to acquaint the entire research community with conflicts of interest in operation. The cases can be used as teaching tools and for probing key questions that are implicated when conflicts are present.

Recommendation: *Through its Forum on Conflicts of Interest in Academe, the AAMC should update and supplement the case studies on a continuing basis and make them available on appropriate websites in order that they may continue to be useful to the research community as means for teaching about conflicts of interest in human subjects research. The AAMC should also make broadly available other quality teaching tools that have been developed by particular institutions on conflicts of interest.*

G. Enforcement

Institutions can send strong messages about institutional culture through the manner in which their policies are enforced, and policies on conflicts of interest are a touchstone. Consistency in enforcement, fairness, and transparency of the process by which enforcement is carried out, the right to appeal adverse determinations, and the full support of institutional administration for the values underlying conflicts policies are all essential components of a culture of integrity, focused on protecting human subjects, research integrity, and the public trust. Institutions should examine their own enforcement practices to assure that these values are appropriately reflected.

APPENDIX A

Model Policy on Institutional Conflict of Interest in Human Subjects Research

[Note: This model Institutional COI Policy represents one expression of the principles and practices recommended in Chapter 2 for addressing Institutional COI. It should not be seen as the recommended model policy but rather as one example of an Institutional COI policy.]

1. Introduction

An institutional conflict of interest (institutional COI) describes a situation in which the financial interests of an institution or an institutional official, acting within his or her authority on behalf of the institution, may affect or appear to affect the research, education, clinical care, business transactions, or other activities of the institution. Institutional COIs are of significant concern when financial interests create the potential for inappropriate influence over the institution's activities. The risks are particularly acute in the context of human subjects research, when the protection of human subjects and the integrity of the institution's research may be threatened. The policy is intended to protect against exposure from these risks as they may affect research performed at or under the auspices of the institution.

An institution, including its officials, must balance many competing pressures. It engages in relationships with a variety of sponsors that may lead to financial benefit for the institution in many forms, including major gifts, royalty payments and equity from licensing intellectual property as well as sponsored educational and research agreements. In addition, university-industry relationships are essential to advance scientific frontiers and enable the commercial development of academic discoveries to the benefit of the public. Nonetheless, while generally part of legitimate educational, research, and business activities, relationships with commercial entities cannot be allowed to compromise, or appear to compromise, the integrity of the institution's primary missions, including the safety and integrity of its research, education, and clinical care. The protection of human research subjects and integrity of the institution must remain of highest priority.

[Comment: This preamble should define whether the institutional COI policy includes the entire university or solely the school of medicine. Consistent with the boundary of the Advisory Committee's charge, this policy is intended to cover the university as a whole but addresses only its human subjects research. The Committee recognizes that institutional COIs can arise in non-human subjects research, clinical care, and education, as well as in purchasing and other university business transactions and the Committee strongly recommends that institutions implement comprehensive institutional COI policies that embrace the full spectrum of the institution's activities.]

In addition to policy provisions, as a general principle in addressing institutional COI, the administrative responsibilities for research, and especially human subjects research, should be separated to the maximum extent possible from the administrative responsibilities for investment management and technology licensing.]

2. Definition of Institutional Conflict of Interest

An institution may have a conflict of interest (“institutional COI”) in human subjects research whenever the financial interests of the institution, or of an institutional official acting within his or her authority on behalf of the institution, might affect—or reasonably appear to affect—institutional processes for the design, conduct, reporting, review, or oversight of human subjects research.

3. Identification of Potential Institutional Conflicts of Interest

The following significant financial and fiduciary interests of the institution warrant formal review of potential institutional COI with respect to human subjects research, as provided in this policy.

- A. Royalties: institutional COI may be present when the institution has the potential to receive significant milestone payments and/or royalties from the sales of an investigational product that is the subject of the research;
- B. Non-publicly traded equity: When, through its technology licensing activities or investments related to such activities, the institution has obtained an equity interest or an entitlement to equity of any value (including options or warrants) in a *non-publicly traded* company that is i) the sponsor of human subjects research at the institution, or ii) the manufacturer of a product to be studied or tested in human subjects research at or under the auspices of the institution;
- C. Publicly traded equity: When, through technology licensing activities or investments related to such activities, the institution has obtained an ownership interest or an entitlement to equity (including options or warrants) exceeding \$100,000 in value (when valued in reference to current public prices, or, where applicable, using accepted valuation methods), in a *publicly-traded* company that is i) the sponsor of human subjects research at the institution, or ii) the manufacturer of a product to be studied or tested in human subjects research at or under the auspices of the institution.

The following significant financial and fiduciary interests of covered officials warrant formal review of potential institutional COI with respect to human subjects research:

[Comment: This section should identify the “covered officials,” that is, those senior administrative officials to which the institutional COI policy applies, e.g., board members, the president/chancellor, provosts and vice provosts, vice presidents/vice chancellors, deans and vice/associate deans, department chairs, division chairs, institute and center directors, IRB chairs, the COI and institutional COI committee chairs, the chair of the institutional biosafety committee, and the chair of the stem cell review committee.]

D. Institutional Officials: When, with regard to a specific research project to be conducted at or under the auspices of the institution, institutional officials with direct responsibility for human subjects research hold a significant financial interest in the commercial research sponsor or an entity that owns or controls the investigational product. “Significant financial interest” is defined for this purpose as being consistent with the institution’s individual conflict of interest policy. In AAMC’s 2002 guidelines for institutional COI, the definition includes the following:

1. An equity interest or entitlement to equity (including options or warrants) of any amount in a *non-publicly traded* company that is i) the sponsor of human subjects research at the institution, or ii) the manufacturer of a product to be studied or tested in human subjects research at or under the auspices of the institution;
2. An equity interest or entitlement to equity (including options or warrants) in excess of the *de minimis* amount (and not including exceptions for certain mutual funds), as defined in the AAMC’s 2001 guidelines for individual financial interests, in a publicly traded sponsor of human subjects research conducted at or under the auspices of the institution;
3. Consulting fees, advisory board fees, remuneration, honoraria, gifts or other emoluments, or “in kind” compensation from a company that is i) the sponsor of human subjects research at the institution or ii) the manufacturer of a product to be studied or tested in human subjects research at or under the auspices of the institution, that in the aggregate exceed the *de minimis* amount as defined in the AAMC’s 2001 guidelines for individual financial interests, or are expected to exceed that amount in the next 12 months;

4. An appointment to serve, in either a personal or representative capacity, in a fiduciary role for a company that is i) the sponsor of human subjects research at the institution or ii) the manufacturer of a product to be studied or tested in human subjects research at or under the auspices of the institution, whether or not remuneration is received for such service. Typically, the appointment will involve service as an officer, director, or other board member of the company.
5. An appointment to serve on the scientific advisory board of a commercial sponsor of human subjects research conducted at or under the auspices of the institution, unless the official has no current significant financial interest in the sponsor or the investigational product and agrees not to hold such an interest for a period of no less than three years following completion of any related research conducted at or under the auspices of the institution.

In addition to those circumstances indicated above, other financial relationships with research sponsors may warrant internal or external scrutiny, depending on the circumstances. Examples are listed below. The list is not intended to be exhaustive. In general, institutions should assess the potential for conflict of interest and weigh the magnitude of any risk to human subjects.

E. Individuals responsible for purchasing: When an investigator, research administrator, or institutional official with research oversight authority participates materially in a procurement or purchasing decision involving major institutional purchases from, or non-routine supply contracts with, a company that sponsors human subjects research at the institution, or whose product is being studied or tested in human subjects research at the institution.

F. Gifts from sponsors: When the institution has received substantial gifts (including gifts in kind) from a potential commercial sponsor of human subjects research or a company that owns or controls products being studied or tested in human subjects research. The following circumstances should be evaluated:

1. Whether a gift is of sufficient magnitude that even when held in the general endowment for the benefit of the entire institution, it might affect, or reasonably appear to affect, oversight of human subjects research at the institution;
2. Whether a gift is held for the express benefit of the college, school, department, institute or other unit where the human subjects research is to be conducted; or
3. Whether any institutional official who has the authority, by virtue of his or her position, to affect or appear to affect the conduct, review or oversight of the proposed human subjects research has been involved in solicitation of the gift.

Although the listed circumstances are potential areas of concern, the goal of this policy is not to preclude the institution from accepting philanthropy from companies that sponsor human subjects research, or that own or control products that are being studied or tested in human subjects research. Rather, the policy is intended to help the institution develop means of identifying and examining such circumstances, and of managing, through disclosure, separation of responsibilities, and as otherwise appropriate, any actual or apparent conflicts of interest that may result. All gifts should be accepted in conformance with these policies and reported to the development office for record-keeping purposes. Faculty members are accountable for adhering to institutional gift policies.

4. Administration of Institutional Conflicts of Interest Policy

[Comment: The responsibility for institutional COI administration should be assigned to an institutional office, and the reporting structure for the office should be to a senior official who can weigh the needs of the human research subjects protection program in particular and of the institution in general. The office will require access to sensitive data, so appropriate consideration to security must be given. The use of the office responsible for individual COI is expedient, given that office's general familiarity with COI issues, although the institutional nature of these issues means that their oversight and resolution will need to be at a high level.]

For purposes of this template, the office responsible for individual COI is used, but whatever office is used, the relationship between the administration of the individual COI policy and the administration of the institutional COI policy should be clearly specified, including whether or not the same committee is used for evaluating and making recommendations and determinations regarding individual COI and institutional COI.

The reporting schedule for covered institutional officials to report their own financial interests should be identified in this section, if it is not separately addressed in the institution's individual conflict of interest policy.]

Administration of institutional COI matters will be handled by the Conflict of Interest Office. In order to make the COI Office aware of potential institutional COI situations and transactions, the following offices should report at least quarterly to the COI Office on interests described in Section 3, above:

- a. Technology transfer office (for licensing arrangements, patents, invention disclosures);
- b. Office of sponsored programs, research administration, or corporate research relations (for sponsored research agreements and products that are the subject of research);
- c. Development office (for gifts);
- d. Grants office (for federal and state grants);
- e. IRB (for human subjects research protocols).

[Comment: Tracking of transactions of the type described in Section 3 would be greatly facilitated by the development of one or more comprehensive databases by the institution.

The issue of using the development office to track gifts will be institution specific. To ensure compliance with tax laws, enforcement of the provision that the gifts carry no quid pro quo, and tracking of potential institutional COI, it is highly recommended that this function be centralized in one or two primary offices. The institution should establish a unified database of gifts and promulgate consistent rules as to how gifts are processed. Institutional policy should provide clear and unambiguous guidelines for distinguishing between gifts and grants with respect to research and for requiring that all gifts should be processed through the development office.]

The COI Office also will be provided by [insert office] with a list of reports submitted by covered institutional officials [add reporting schedule here]. These COI reports will be reviewed at least annually by the COI Office, and in the event they create a potential institutional COI, by the institutional COI Committee.

5. Composition of the Institutional Conflicts of Interest Committee

[Comment: In order to clarify the relationship between the administration of the individual COI policy and the institutional COI policy, this section must specify whether or not the same committee is used for evaluating and making recommendations and determinations regarding COI and institutional COI. If separate offices are to be established, the institutional COI composition must be defined in this section.]

The institutional COI Committee will consist of at least seven members appointed by the institution's President/Chancellor (or his/her designee), of whom at least two will be members of the public with no active transactional relationships with the institution. One of the public members should have no institutional affiliation at all. In case of the public member(s) affiliated with the institution (for example, alumni), care should be taken that neither they nor their immediate family members are on the institution's payroll. At least two members of the institutional COI Committee should be appointed from the standing individual COI Committee(s). A quorum will consist of four voting members, at least one of whom should be a public member.

Members of the institutional COI Committee should be free of responsibility for institutional supervision of the human subjects research protection program. They can, however, be principal investigators on human subjects research projects. They should abstain from institutional COI Committee business when they have a personal COI or involvement in institutional COI that relates to a research proposal under review, as provided by institutional policy.

[Comment: The composition of the institutional COI Committee as described above is arbitrary and should be consistent with the size of similar committees at the institution. It may be the same as, overlapping with, or different from the membership of the COI committee. The use of public members is important for the credibility of the institutional COI process, and the appointment of more than one public member may emphasize the institution's goal of meaningful oversight, but the appointment of outside members may not be feasible in some institutions because of particular institutional governance provisions or policies.]

6. Review and Management of Institutional Conflict of Interest

[Comment: This section presumes that the institution has chosen to assign responsibility for administration of the institutional COI policy to its COI office (the office responsible for administering the institution's policy on individual COIs). It further presumes that the COI Office conducts a preliminary review and then transmits potential institutional COI cases to the institutional COI Committee that the institution has chosen to establish, instead of using the same committee that is responsible for reviewing potential individual COI. These choices will be institution-specific but should be specified.]

When a potential institutional COI that involves a human research project is identified, the COI Office will notify the IRB and the sponsored programs office (if the institutional COI involves a sponsored project). The COI Office will review the potential institutional COI and prepare a document describing the case and the nature of the real or potential institutional COI. In cases involving presumptive institutional COI, the case document will be referred to the institutional COI Committee.

[Comment: The institution may choose to specify categories of institutional COI, including presumptive institutional COIs that present no risk to the integrity of research and no risk for human subjects and can be handled administratively with defined management plans and documentation. Such categories should be reviewed periodically by the institutional COI Committee. An example of a low level of concern is the case where the chair of a department holds stock in the sponsor of human subjects research conducted in some other department within the medical school but has no involvement in the research or administrative responsibility for it.]

When a potential institutional COI is identified, the institutional COI Committee shall apply a **rebuttable presumption** that either the financial interest should be eliminated or the human subjects research should not be conducted at the institution. The presumption may be rebutted if the circumstances are deemed compelling by the institutional COI Committee, and provided that the Committee approves an effective institutional COI management plan. Whether the presumption is successfully rebutted will depend in each case upon an analysis of:

- a. the nature of the science,
- b. the nature of the overlapping interests,
- c. how closely the interest is related to the research,
- d. the degree to which the interest may be affected by the research,
- e. the degree of risk that the research poses to human subjects and the integrity of the research, and
- f. the degree to which the institutional COI can be effectively managed.

The Committee should consider whether the institution is uniquely qualified, by virtue of its attributes (e.g., special facilities or equipment, unique patient population) and the experience and expertise of its investigators, to conduct the research and safeguard the welfare of the human subjects involved.

If it is determined that there are compelling circumstances for allowing the research to proceed in the presence of the institutional COI without elimination or significant reduction of the financial interest, those circumstances should be documented in the institutional COI Committee report on the matter. Management plans for approved institutional COI arrangements should be designed effectively to address: 1) the nature of the conflict; 2) the specific risks to human subjects; 3) the perceived risk to the integrity of the research as a result of the conflict; and 4) the perceived risk to the reputation of the institution.

One or more of the following management strategies should be used:

- a. Disclosure of the institutional COI in the informed consent process;
- b. Where the institutional COI involves a senior official, formal recusal of the conflicted official from the chain of authority over the project and possibly also from authority over salary, promotion, and space allocation decisions affecting the investigator, as well as communication of the recusal arrangements to the official's superior and colleagues. (Note that recusal is not an effective management strategy when the individual, by virtue of conflicts arising from personal financial holdings, would be precluded from fulfilling the responsibilities of his or her position. In such cases, the best interests of the institution may necessitate that the individual divest the interests or vacate the position.)
- c. Where the institutional COI involves a senior official, designation of a "safe haven" (e.g., a non-conflicted senior individual) with whom the investigator can address institutional COI-related concerns;
- d. Use of an external Institutional Review Board (since most institutional IRBs are composed of faculty and staff from the institution);
- e. External monitoring of the study, particularly endpoint assessments;
- f. Use of an external DSMB or similar review board to evaluate the design, analytical protocols, and primary and secondary endpoint assessments, and to provide ongoing evaluation of the study for safety, performance issues and the reporting of results;
- g. Disclosure of the institutional COI in public presentations and publications;
- h. Disclosure of the institutional COI to other centers in a multi-center trial.

[Comment: Chapter 3 of this Report provides a full discussion of management techniques.]

The report and the recommended decision should be transmitted to [insert decision-maker here, e.g. dean, vice president, etc.] for final determination. Approval of management plans will be initially by school deans (or their designees) or by the senior institutional research officer, although the final authority rests with the President and Board of Trustees. Appeals from initial decisions will follow regular institutional appeal procedures. Review of compliance with management plans will be performed by [insert name of institution office].

The COI Office should provide the institutional COI Committee's decision and the underlying report to the IRB and the sponsored programs office (if the institutional COI involves a sponsored research project) so that the IRB review of the project can consider the deliberations and recommended handling of the institutional COI, and so that the sponsored research office can meet its applicable reporting obligations.

7. Implementation

Each institutional COI management plan should state specifically who will be responsible for the plan's implementation. Adherence to the management plan will be evaluated by the institution's [insert office name].

[Comment: Issues related to the oversight of implementation should be tailored to the offices at the Institution responsible for monitoring compliance. Institutions may wish to define sanctions for those officials who fail to comply.]

APPENDIX B

Analyzing Cases Involving Potential Conflicts of Interest in Human Subjects Research: Template and Compendium of Cases

1. Template for Analyzing Cases Involving Potential Conflicts of Interest in Human Subjects Research

This short-form analysis template encapsulates the major elements required for a thorough and effective analysis of financial conflict of interest (COI) situations. It outlines the steps that lead from the initial assessment of the fact pattern, to a risk-benefit analysis and finally to a review of options for resolution or management.

I. Description of Research. Conflict of Interest Committee (Committee) members should have a description of the proposed research with sufficient detail so that they understand where points of conflict might arise. The description could be provided in the form of a case report with supporting documents, including the research protocol and related protocols if appropriate; agreements between key personnel and external entities; information about patents, licenses, and royalties, and other factors that may aggravate possible conflicts in the research project. For example, the description should indicate whether the research includes human subjects and how the subjects are treated by the protocol; e.g., whether the procedure involves blood draw or tissue sample, major surgical procedure, or taking a drug with few side effects for a new use.

II. Description of External Interests. Committee members should have a description of the external interests held by the individual, whether financial or other, to clarify the extent to which the individual with a financial interest is conflicted. Information could include, for example:

- a. The nature of the external company or other entity and its relationship to the research: e.g., whether the company is a proposed sponsor of the research project, a vendor of equipment, supplies, or services for the research.
- b. The role in the research project of the individual with the interest: whether he or she is a principal investigator, collaborator, spouse of investigator, or author to determine the key personnel in the project.
- c. The role in the external company or other entity of the individual with the interest: e.g., whether he or she provides services as a consultant, officer, scientific board member or chair, including the amount of compensation to be paid for the services.
- d. The role in the university of the individual with the interest: e.g., whether they are a faculty member, department chair, graduate student or fellow, administrator, or research staff member.

III. Relation of External Interests to Research and Identification of Potential Conflicts. Based on the facts provided under I and II, Committee members should determine how the external interest of an individual relates to the person's research and whether a specific conflict of interest exists either under institutional policies or under state or federal regulations or guidelines.

IV. Risk-Benefit Analysis. If a conflict of interest is identified, the Committee should proceed to perform a risk-benefit analysis to determine whether the conflict of interest should be managed, reduced, or eliminated. Examples of areas for potential risks and possible benefits include:

- a. Risks to the human subject recruited to or participating in the research: the analysis should determine the extent to which the conflict could increase or add risk to the human subject, depending on how the conflicted individual recruits and treats subjects under the protocol.
- b. Risks for bias of the data by the conflicted individual: the issue for analysis is the extent to which the conflicted individual could compromise the integrity of the data.

- c. Risks for the appearance of a conflict of interest: determination of the risk from the appearance of a financial conflict of interest is important regardless of whether an actual conflict exists or is managed.
- d. Risks to the reputations of the conflicted individual and the institution: it is important to consider the extent to which the reputations of the conflicted individual or institution could be damaged, even if the conflict is managed.
- e. Benefits to medicine, science, and public health that could accrue if the research is allowed to be conducted as planned. Alternately, benefits might be lost if the research is not permitted to go forward: the issue for analysis is the extent to which the benefit outweighs the associated risks if the research is allowed to proceed.

V. Reduction of Elimination of the Conflict. The Committee should determine whether the conflicted individual can participate in the research without further action. If not, the Committee should determine whether the conflict might be reduced or eliminated to allow the research to go forward. Methods could include:

- a. Divestiture of the external interest;
- b. Divestiture of the management of external interests;
- c. Refusal of any external compensation; or
- d. Reduction in the amount of external compensation.

VI. Rebuttable Presumption and Compelling Circumstances. In cases where the conflicted individual does not wish to change the extent of his or her external services or level of compensation, there is a presumption that the conflicted individual should not conduct the human subjects research. This presumption is rebuttable, if the Committee determines that compelling circumstances justify the participation by the conflicted researcher in the research under specified conditions.

VII. Management of the Conflict. If it is determined that, due to compelling circumstances, the participation of a conflicted individual can be justified, an effective conflict management plan must be designed by the institution and agreed to by the conflicted person. Depending on the facts of the case, the following are some of the elements of a management plan that could be appropriate:

- a. Sufficient disclosure of the conflict to other participants on the research team, human research subjects, the academic supervisor, and peers and the public in all forms of presentation and publication;
- b. Steps to ensure integrity of the data;
- c. Steps to protect human research subjects;
- d. Steps to protect students, trainees, and others under supervision;
- e. Steps to address conflicted administrators and supervisors.

2. Compendium of Cases Illustrating Conflicts of Interest in Human Subjects Research

In the consideration of each of the following cases, it will be useful to keep these key concepts and definitions in mind.

A conflict of interest exists when a significant financial interest (or other personal interest) may compromise, or have the appearance of compromising, an investigator's judgment in conducting or reporting research. When the research includes participation of human subjects, the AAMC guidelines provide the "rebuttable presumption" that the conflicted investigator should not be allowed to conduct the research.

According to applicable federal regulations, significant financial interests are anything of monetary value above a threshold in a company, research sponsor or other company or entity when those interests appear to be reasonably related to the research.

Federal regulations must be observed whenever a research project includes support from federal appropriations. PHS has determined applicable asset categories and minimum thresholds as follows:

1. payments (actual or in kind) for services to the company (such as consulting fees or honoraria) of more than \$10,000 in a single year;
2. an equity interest (such as stocks, stock options, or other ownership interests) that exceeds \$10,000 in fair market value or represents an ownership interest greater than 5 percent in a single entity;
3. intellectual property rights (patents, copyrights, or royalties from such rights);
4. a management position in a company or other entity, such as board member, director, officer, partner, or trustee.

In addition to incorporating applicable federal regulations, most institutions have also adopted some or all of the AAMC recommendations governing conflict of interest in clinical research into their institutional policies. Many institutions apply the AAMC recommendations to all research conducted at the university, regardless of intra-institutional differences and of the source of funding. Others, especially public institutions whose employees are governed by state conflict of interest regulations, have imposed more stringent thresholds, including zero-based reporting of financial assets. Users of these case studies should be sure to take their institutional policies into consideration.

Case 1: Consulting

A. Description of the research:

Dr. Smith proposes to be a local site principal investigator (PI) of a large, Phase III, multi-center trial to test a new statin in human subjects who cannot lower their cholesterol by diet and exercise alone. CardioX, the manufacturer of the statin and a publicly-traded company, is the sponsor of the study. The university (University) where Dr. Smith is a faculty member will be paid a fixed fee for each subject enrolled. The study will be administered by a contract research organization (CRO), and a Data Safety Monitoring Board (DSMB) has been established. CardioX will submit results of the study to the FDA for marketing approval. Dr. Smith's site is one of 50 participating in the study and is expected to enroll 2-3% of the subjects.

B. Description of the external interests:

Dr. Smith is a member of CardioX's scientific advisory board. He attends four meetings each year and is paid a total of \$8,000 for the advice he provides to the company. The work of the scientific advisory board is not directly related to the subject of the study and CardioX has asked that Dr. Smith continue acting as an advisor, while also serving as site-based PI of the study.

C. Does a specific conflict of interest exist?

Because the compensation received by Dr. Smith from the research sponsor falls under the threshold used by some institutions to define a conflict of interest, and because he does not hold a leadership position on the scientific advisory board, the research could be allowed to proceed. However, some institutions require disclosure of all external financial interests for clinical research and have a "rebuttable presumption" that prohibits an investigator who has a financial interest in the research sponsor from conducting the research without a compelling justification for an exception.

D. Risk-benefit analysis:

Where institutional policies might allow this research to be conducted by Dr. Smith under certain circumstances, what are the risks of this arrangement?

- 1. Is there an increased risk to human subject safety? Is there an increased risk of failure to adhere to the inclusion/exclusion criteria of the protocol? Might he over-state the potential benefits of the drug while soliciting consent?*

Institutions often subsidize clinical research, and assuming that it is doing so in this case, the fixed fee payment to University is unlikely to benefit the institution or Dr. Smith. The amount of personal compensation Dr. Smith receives for his consultation is modest. However, even though his consulting for CardioX is not in the area directly tied to his research, the relationship could create a sense of reciprocity. Since Dr. Smith does not own equity, an outcome that favors the statin would not directly increase his compensation but conceivably Dr. Smith's relationship and continued consulting with CardioX could be enhanced by a favorable outcome. Taking all that into account, a COI committee could still find that the risks to human subjects are not likely to be increased as a result of Dr. Smith's consulting arrangement.
- 2. Is there a risk to data integrity?*

The risk is low. Dr. Smith has no control over the study protocol. A CRO is monitoring the data collection practices at the sites, and the DSMB reviews the data on a quarterly basis.
- 3. Is there a risk of an appearance of a conflict of interest?*

Yes, there is such an appearance. Even though Dr. Smith might consider the \$8,000 compensation to be a modest amount and unrelated to his research, and even though the data are analyzed by others, the public could have a different view of his financial relationship with the research sponsor. This perception could be enhanced especially if adverse events were to occur, in light of the conflicts of interest already reported in the clinical research and marketing of statins. University might not have an opportunity to present the mitigating facts.
- 4. Could the outcome of the study benefit the public?*

Yes, assuming that any actual and perceived conflicts of interest are effectively managed.

E. Could Dr. Smith be allowed to pursue this research proposal while serving as a paid consultant to CardioX?

Dr. Smith could be required to give up his consulting with CardioX or continue to do it for no compensation in order to eliminate the COI. If he declines to sever the consulting relationship with the company, Dr. Smith could still be allowed to serve as site PI with a COI management plan unless the institution's COI policy prohibits arrangements of this type. The combination of a public benefit and low risks could overcome the prohibition in the "rebuttable presumption" test if an effective management plan is designed and put in place. The institution could consider imposing one or more of the following management conditions:

1. At a minimum, Dr. Smith would have to disclose that he is paid by the research sponsor as a consultant in all relevant publications, presentations, and consent forms and to others on the study team.
2. All publications and presentations must be written by the investigators, not by a CardioX ghost writer.
3. Dr. Smith would not be able to participate in the process of selecting, recruiting and obtaining consent from research participants.
4. Dr. Smith would be expected to inform the CRO and DSMB of his conflict of interest.

Case 2, Part A: Licensing, Leadership

A. Description of the research:

In animal studies in his laboratory, Dr. Rose, Professor and Chief of the Division of Gastroenterology in the Department of Medicine at University, has identified a biomarker that he believes may be important in identifying precancerous intestinal lesions. He has also developed a method for “lighting up” the biomarker so that it can be detected by imaging. His preliminary work suggests an association between a significant presence of the biomarker in the small intestine and the likelihood that the human subject will eventually develop gastro-intestinal (GI) cancer. Dr. Rose now proposes to be the PI on an NIH grant to test his hypothesis.

In the protocol, a surgeon will remove a tiny sample of small intestine tissue from patients who are undergoing GI surgery for diagnoses other than cancer. Dr. Rose will initially test the tissue samples for the biomarker and, over the next three years, will correlate the results of his assay with those patients’ clinical progress. If a correlation between a significant presence of the biomarker and diagnoses of cancer is found, he will have established the predictive value of the assay. According to the protocol, consent will be solicited from the surgical patients by a research coordinator, and Dr. Rose will have no role in the surgery. His laboratory will receive from the surgeon the harvested intestinal tissue for the assay and also the clinical data to establish a baseline.

B. Description of the external interests:

The University has licensed Dr. Rose’s assay for lighting up the biomarker in intestinal tissue to Diagnocorp, a large company that develops diagnostic kits. The terms of the license include modest annual fees and post-marketing royalty payments of 4% of sales. Under the University’s intellectual property policy, Dr. Rose is entitled to 35% of University’s income from the licensed assay, and his division is entitled to 30% of the income.

C. Does a specific financial conflict of interest exist?

The answer depends in part on whether the project is considered clinical research. Guidance from national associations of higher education recommends that institutional policies should prohibit the conduct of clinical research in the presence of an investigator’s significant financial interests and federal regulations recognize royalties as potentially significant financial assets. Some universities might not consider this protocol to involve clinical research because they take the position that clinical research must involve experimental procedures performed on the subject *in vivo* and will rely on their IRB to determine whether the potential benefit of the study justifies any risk that might be associated with the removal of the tissue sample. Other universities would conclude that this protocol involves clinical research, and that a conflict of interest exists. Accordingly, their COI Committee would be expected to undertake a thorough risk-benefit analysis.

D. Risk-benefit analysis:

1. *Is there a risk to the safety of human research participants? Is there an increased risk of failure to adhere to the inclusion/exclusion criteria of the protocol? Is there a danger of overstating the potential benefits of the assay while soliciting consent?*

The risks to subjects resulting from the removal of the tissue sample are determined by the IRB and are distinct from the risks that might result from Dr. Rose’s financial interests in the outcome of the study. The overall risk to the participating subjects is very low, since Dr. Rose is not participating in the selection, recruitment, or consent process or in the surgery.

2. *Is there a risk to data integrity?*

The potential risk is that the promise of sales of diagnostic kits could influence Dr. Rose’s judgment in the analysis of data and lead him to overstate the success and utility of his diagnostic technique. However, the expression of the biomarker in each sample and diagnosis of cancer is to be handled by an objective third party physician, over a period of three years. Not only does the data collection appear secure, but bias in the interpretation of the data likely would be apparent.

3. *Is there a risk of an appearance of a conflict of interest?*

The appearance of a financial conflict is a potential risk in this case but through public disclosure and other arrangements that risk can be largely mitigated.

4. *How does Dr. Rose's role at the University affect the COI review?*

As Chief of the Division of Gastroenterology, Dr. Rose's administrative decisions about faculty, staff, students, and purchasing could be influenced by his desire to produce a successful assay and to receive royalties. He might also be tempted to involve faculty, students and staff in his research in inappropriate ways, or show favoritism in his decisions regarding salary and promotion. Care should be taken to prevent the possibility that the division's share of royalties could be channeled to Dr. Rose's own advantage. However, most departments have internal controls in place, including oversight by the chairperson, to handle conflicts of interest such as these. It is equally important, though, to avoid the appearance of an administrative conflict of interest, on behalf of the public as well as of those in the division, who might suspect uneven treatment due to Dr. Rose's personal financial interests.

5. *What are the benefits if this study is allowed?*

There is significant benefit in moving a potentially valuable diagnostic technique into commercial development.

E. Should Dr. Rose be allowed to conduct this study in light of the licensing of his invention to Diagnocorp?

Dr. Rose could decide to forego the revenue from royalties that will come to himself and his division in order to avoid any appearance of conflicts. Even if he chooses not to do that, the Committee could still determine that this study can go forward because with appropriate management of the conflict of interest, the risks are low. The potential for conscious or unconscious bias as a result of the promise of future royalties may exist, but Dr. Rose's ability to manipulate results of the study will be limited, particularly if there is oversight.

Unless the institution's COI policy categorically prohibits arrangements of this type, the institution should consider imposing one or more of the following management conditions:

1. Require Dr. Rose to disclose his financial interest in future fees and royalties, based on the respective licensing terms in all relevant publications, presentations, and consent forms; to others on the study and surgical teams; to his department chair, the faculty in his division, the trainees participating in the project and to others on the study and surgical teams.
2. Require the chair or designee to review the interactions of Dr. Rose with trainees and to provide them with access to senior disinterested individuals (e.g., the graduate program director) if they believe that Dr. Rose's financial interests are interfering with their research or training.
3. Require the department chair or designee to review Dr. Rose's administrative decisions to ensure equitable compensation, performance reviews, promotions, and other relevant decisions affecting the division and his laboratory. If royalties accrue to the division, it would be advisable to conduct an independent review of Dr. Rose's use of those funds, to ensure his compliance with University purchasing and other ethics requirements.
4. Require a knowledgeable, disinterested individual to oversee the collection, analysis, and reporting of the study data.
5. Designate one or more knowledgeable, disinterested individuals as a "safe haven" for any divisional faculty members and staff who have concerns about the arrangement.

Case 2, Part B: Variation of the Facts

A: Description of the Research:

In addition to harvesting the intestinal tissue sample from patients in the course of clinically-indicated surgery, Dr. Rose's protocol also requires the surgeon to inject a radioactive compound in the intestine wall for later imaging detection of the biomarker. This will permit sophisticated imaging of the small intestine.

B. Risk-benefits analysis:

1. *Is there a risk to human subject safety?*
The IRB could find that this injection presents more risk to human subjects because, although not life-threatening, injection of the radioactive compound and later imaging might cause short- and medium-term harm to subjects. However, the risk that Dr. Rose's conflict would influence the conduct of the protocol with patients is not changed.
2. *Is there a risk to data integrity?*
The protocol introduces a new endpoint; images of the intestinal wall will be analyzed. However, the image analysis will be done by an unconflicted, independent radiologist who does not report to Dr. Rose. There is no significant change in the risk to data integrity.
3. *Is there a risk of an appearance of conflict of interest?*
The increased risk to human subjects could heighten the appearance of a conflict of interest.
4. *Is the risk of a supervisory conflict of interest magnified?*
The supervisory conflict of interest remains unchanged.

C. Should Dr. Rose be allowed to conduct this study, with slightly increased risk to human subjects, in light of the license of his invention to Diagnostics Corp?

The protocol involves a contrast agent being injected into human subjects, who will be imaged for presence of the biomarker. If the research is prohibited by university policy but the policy recognizes the concept of a "rebuttable presumption," the COI Committee could evaluate whether some of the key factors in the case could serve to overcome the presumption against allowing Dr. Rose to serve as principal investigator. Among the key decision factors are whether he has unique skills or qualifications needed in the protocol; whether University is the only place where the study could be conducted; or whether another independent, unconflicted investigator could be the principal investigator. The Committee could recommend a management plan including some or all of following elements.

1. The plan should include some or all of the previously listed components with the addition of disclosure of Dr. Rose's financial situation to the radiologist.
2. The plan might allow Dr. Rose to serve as co-investigator, but would also appoint an unconflicted, independent principal investigator from outside the division and direct the new PI to review and oversee data collection and analysis.

Case 3: Start-up Company

A. Description of the research:

Dr. Sellers, Assistant Professor of Medicine in the Hematology/Oncology Division at University, is a clinical investigator of ovarian cancer. She discovers a protein in ovarian cancer cells and shows that a monoclonal antibody (MAB) to it can reduce the progression of cancer in a mouse xenograft model. No biotech company has so far licensed the MAB from University, and the NIH did not fund a proposal for Phase I studies in humans for a possible proof of principle. However, Dr. Sellers is a very effective “champion” for this technology and has raised local venture capital money to start a small biotech company to further develop the project. According to University policy, Dr. Sellers receives approval to start up the company, and University licenses the MAB technology to Dr. Sellers’s start-up company. The company proposes to sponsor a Phase I clinical trial in which Dr. Sellers will inject the MAB into human subjects with ovarian cancer to study the effect of the antibody on the progression of the cancer.

B. Description of external interests:

Appropriately, Dr. Sellers was only minimally involved in the license negotiations between the company and University. Review of the company structure indicates that Dr. Sellers has obtained 100,000 shares of founders stock. She is not an officer, or a member of the Board of Directors or the Chair of the Scientific Advisory Board of the company. However, she is a member of its Advisory Board and she receives a payment of \$30,000 a year for her service on it.

C. Does a specific financial conflict of interest exist?

Yes. As founder of the company that uses technology generated in her laboratory under a license from the University, Dr. Sellers has a significant financial and intellectual interest in the outcome of this study that could influence her judgment in the conduct of the trial and in the subsequent evaluation of the resulting data. Guidance from national associations of higher education and many institutional policies on conflict of interest would prohibit her participation as PI, unless the “rebuttable presumption” test could be overcome.

D. Risk-benefit analysis:

Where institutional policies might allow this research to be conducted under certain circumstances, what are the risks of this arrangement?

1. *Is there an increased risk to human subject safety? Is there an increased risk of failure to adhere to the inclusion/exclusion criteria of the protocol? Is there a danger of over-stating the potential benefits of the MAB while soliciting consent?*
Because of Dr. Sellers’ proposed direct involvement in the selection, recruitment, and consent processes of the study and her leading role in administering the MAB, there is risk that her financial interests could influence her judgment in the selection, recruitment, and consent process. She could, for example, select and recruit patients and assign them to experimental groups in ways that might enhance her financial interests but that would not be in the best interests of the patients. She might inform patients about the risks of the study and obtain their consent to participate in it without full disclosure of the scientific facts or of her personal financial interests.
2. *Is there a risk to data integrity?*
Yes, Dr. Sellers would be in a position to influence the outcome of the trial in ways that are favorable to her financial interests and those of her company by selecting patients who do not satisfy enrollment eligibility standards and by interpreting the data in favor of the effectiveness of the MAB.

3. *Is there a risk of an appearance of a conflict of interest and reputational damage?*

Ovarian cancer patients are seriously ill and expect the judgment of their physicians to be based on scientific evidence and clinical experience. Even the appearance that Dr. Sellers could be influenced by her conflict to manipulate her patients and the clinical trial for personal gain could be harmful to her reputation and that of University. The risk of adverse events and unsatisfactory results is increased by the fact that the safety, effectiveness, and side effects of the MAB are unknown. Dr. Sellers' conflict of interest as PI is both a real and an apparent conflict of interest. By conducting this trial, she could place herself and the institution at risk for reputational damage, especially if an adverse event were to occur. Such damage would be difficult to repair after the fact even if no fault were found with her or with the institution's actions.

4. *Could the outcome of the study benefit the public?*

Though speculative at this point, the MAB could prove effective in treating ovarian cancer. The hope of successfully treating very seriously ill patients places the potential benefits in a positive light. Nevertheless, at this stage, the project still lacks important peer endorsement. Preliminary results have not provided sufficiently strong evidence for the NIH to involve itself by supporting further research.

E. Should Dr. Sellers be allowed to conduct this study in light of her conflict of interest?

Based on University policy and national guidelines, the Committee will most likely restrict or outright prohibit Dr. Sellers' ability to conduct this trial. In that case, she could choose to eliminate the COI by reducing or giving up her financial interests. Alternately, University could choose to determine whether Dr. Sellers can conduct the trial under an exception to the "rebuttable presumption". That test recognizes that it often takes a 'champion' to move a concept to proof of principle, but being a 'champion' is not by itself a compelling justification to overcome the "rebuttable presumption" standard. It does not appear that unique skills are required to conduct this trial, and thus a key indicator of the "rebuttable presumption" test would not be met. Further, the evaluation and assessment phases of the project do not appear to require unique skills, though the PI should be experienced in assessing the progress of ovarian cancer in human subjects.

The Committee could suggest that the company sponsor this trial at another institution. If University considers it to be in its interest to retain a close relationship with the start-up company or the trial, the Committee could recommend that the trial go forward at University, but only on condition of removing Dr. Sellers as PI. In the latter case, the required management plan could include the following conditions:

1. Identify an independent, unconflicted faculty investigator who can be appointed as the PI. In this case, independence would be demonstrated by ensuring that the new PI is not a close friend or relative of Dr. Sellers, has no reporting line to her and is not subject to her approval authority.
2. Mandate that all members of the laboratory/project team disclose their financial relationships to all human research participants. Disclosure of respective financial interests would have to be made in all verbal presentations and written publications on the subject.
3. Restrict Dr. Sellers' role to that of co-PI or collaborator.
4. Preclude Dr. Sellers' role in the selection, recruitment, or consent process and interaction with human subjects.
5. Assign responsibility for the clinical assessment of the progress of the human research participants only to the new PI or designated others. The role of Dr. Sellers or her laboratory staff in this trial would be restricted to the analysis of blinded data.
6. If University holds equity in the start-up biotech company it should find a way to address the institutional conflict of interest, perhaps by eliminating its holdings in the company before the clinical trial takes place.

Case 4, Part A: Stock Option Ownership

A. Description of the research:

Dr. Roberts, Professor of Pediatrics at University proposes to be the principal investigator on a multi-site, Phase II clinical trial to test the safety and immunogenicity of an inactivated vaccine for respiratory syncytial virus (RSV) in a pediatric population. Pediatric human subjects would be injected with the vaccine and compared to a control population over time to determine whether the vaccine protects pediatric subjects from RSV-bronchiolitis.

The proposed sponsor of the research is SuperVax, a publicly-traded small biotech company that makes the vaccine. RSV is the most common cause of bronchiolitis and pneumonia among infants and children under one year of age and is also known to cause illness in elderly people and in people who are compromised by other diseases. Dr. Roberts is already the PI of a large NIH-funded R01 grant focused on the basic immunologic properties of RSV and he plans to analyze specimens generated from the SuperVax RSV clinical trial as part of the R01 project.

B. Description of the external interests:

Dr. Roberts has stock options in SuperVax. The company's stock is currently trading below the exercise value of his options.

C. Does a specific financial conflict of interest exist?

Yes. Ownership of equity in the company that manufactures the study drug/device is recognized to be a significant financial interest. The magnitude of the conflict is increased when the company also sponsors the research, even though at this time the stock holder's equity interest cannot be easily valued. If the study proves the vaccine to be safe and effective and if it is subsequently licensed to a larger company for marketing, the value of Dr. Roberts' equity could increase considerably. This possibility could influence his judgment in the conduct of the clinical trial. While the need for additional RSV specimens could motivate Dr. Roberts to conduct the RSV trial to benefit his NIH sponsored research, the relationship is not a financial conflict of interest, and a COI committee should ask for more information to determine whether other conflicts are present.

D. Risk-benefit analysis:

Where institutional policies might allow this research to be conducted under certain circumstances, what are the risks of this arrangement?

1. *Is there an increased risk to human subject safety? Is there an increased risk of failure to adhere to the inclusion/exclusion criteria of the protocol? Is there a danger of over-stating the potential benefits of the drug while soliciting consent?*

Dr. Roberts' ownership of stock and desire for the success of the company could influence his enrollment of patients into control and experimental groups and it could influence his clinical assessment of patients in both groups to favor the success of the vaccine. He might realize revenue up front with the commercial licensing of the vaccine by Super-Vax to a number of larger companies well before the long-term effects of the vaccine are properly understood.

2. *Is there a risk to data integrity?*

The risk inherent in loss of data integrity may be greater in this case than the health risk to individual research participants. Dr. Roberts' desire for increasing the value of the company stock and his own financial interest could influence how he records and interprets the data from the experimental and control groups of pediatric subjects to favor success of the vaccine.

3. *Is there a risk of an appearance of a conflict of interest?*

A risk is definitely present, and it is greater because the human subjects are infants and children. Even with management of the COI, the public might not be convinced that manipulation of data can be prevented and could question the integrity of the institution and the investigator in conducting such trials involving children where there is the possibility of financial gain.

4. *Could the outcome of the study benefit the public?*

Yes. RSV is an enormous health problem and an effective vaccine would prevent serious illness and economic loss for many children and adults.

E. Could Dr. Roberts be allowed to pursue this research as PI in view of his conflicts?

If Dr. Roberts does not agree to divest his stock options, the AAMC guidelines and the policies of many institutions of higher education would prohibit his participation in this clinical trial as PI because of his financial conflict of interest and the fact that the circumstances would not justify an exception to the “rebuttable presumption” test. Since the trial is a multi-site study, it is apparent that Dr. Roberts is not uniquely qualified to serve as PI. However, because of the potential for great public benefit, the institution could consider imposing one or more of the following conditions before allowing the trial to proceed:

1. Require the substitution of an unconflicted, independent principal investigator. Financial disclosures by the new PI to human subjects or their parents should also be required.
2. If Dr. Roberts were to participate as a co-investigator, a minimum precondition would be his disclosure of his financial interests in the research sponsor and manufacturer of the vaccine. This information would have to be included in all publications, presentations, and consent forms relevant to the study and shared with others on the study team.
3. Require all publications and presentations to be written by the investigators, rather than by a SuperVax ghost writer.
4. Prohibit Dr. Roberts from having any role in the patient selection, recruitment, or consent process and no interaction with them at later stages of the trial or during the assessment phase.
5. Require the clinical assessment of the human subjects data to be performed by the new PI or designated others; any data analysis done by Dr. Roberts or his laboratory would be restricted to blinded data.

Case 4, Part B: Junior Colleague/Investigator

A. Description of the research and external interests:

Dr. Roberts proposes that Dr. Brill, a colleague in his department, serve as the principal investigator on the study. Dr. Brill is an assistant professor who needs publications to ensure her promotion. The SuperVax grant to the University includes in its budget 10% support of Dr. Brill’s University salary based on her percent effort devoted to the research. She does not have a consulting or equity relationship with the company.

B. Does a specific conflict of interest exist?

Dr. Brill does not have a direct financial conflict of interest since her salary is paid by the University, not directly from SuperVax.

C. Could Dr. Brill be allowed to pursue this research proposal?

There is no risk in her participation in the proposed research as long as she is independent of Dr. Roberts. If she neither reports to him, nor is supervised by him, she cannot be influenced by him in the conduct of the trial.

Case 5: Stock and Patent

A. Description of the research:

Drs. Weiss and Gruen, faculty members in the Pulmonary Division of Medicine, and Dr. Jones, Associate Professor of Pharmacology at University, propose to conduct a Phase II, randomized, double-blinded, placebo-controlled trial funded by the Cystic Fibrosis Foundation. It is the aim of the study to test the efficacy of an orally-administered drug (NAC or N-acetyl cysteine) in reducing lung inflammation in cystic fibrosis (CF) patients. Drs. Weiss and Gruen plan to be the co-principal investigators and Dr. Jones plans to be a collaborator. The hypothesis is based on their previous findings that glutathione levels are decreased in CF patients, that this decreased glutathione level plays a role in lung inflammation, and that NAC boosts glutathione levels in blood neutrophils.

Animal studies suggest that NAC will reduce lung inflammation in cystic fibrosis (CF) patients. The literature indicates further that neutrophils are thought to play a key role in the lung disease of CF patients. Drs. Weiss and Gruen will administer the drug to CF patients, extract blood samples and expedite them to Dr. Jones' laboratory to assess the patients' clinical response to the drug. Dr. Jones will analyze the intracellular glutathione levels in neutrophils derived from the blood samples, using multiparameter flow cytometry (FACS) methods that were developed in his lab for measuring glutathione in neutrophils.

Time is critical as samples must be analyzed within an hour after collection because neutrophils change their functional properties once they are removed from the body. Dr. Jones' laboratory has also developed new protocols that prevent artifactual activation of neutrophils. Thus samples must be collected from the site where Dr. Jones works. The excessive transport time to another site and the agitation of the samples would lead to activation of the neutrophils, thereby potentially skewing results.

B. Description of the external interests:

Dr. Jones has stock in the privately-held start-up company that will supply the NAC compound, and University has filed a patent for the use of NAC in CF with Drs. Weiss, Gruen, and Jones as inventors. The company is the only reputable company that currently makes NAC, but it has no proprietary interest in its use for this purpose. In return for providing the compound for the study, the company requires a materials transfer agreement that licenses University's NAC patent to the company. If the trial is successful and if the company markets NAC for treating CF patients, the University and the inventors will share a royalty stream.

C. Does a specific conflict of interest exist?

All three investigators have research related financial conflicts of interest. Dr. Jones owns stock in the company that makes the compound and he could also benefit financially from royalties received from licensing if the treatment is successful. The other two investigators stand to benefit only from potential royalty revenues.

Since the company is privately held, Dr. Jones' stock holdings cannot be easily valued. However, equity in a start-up company could represent a significant financial interest, especially if the results of the research were favorable and if the company continues to sell NAC for this use. AAMC guidelines recommend that investigators who hold equity in a start-up company that is closely involved in clinical research should be prohibited from engaging in the research unless the "rebuttable presumption" test can be overcome by a justification for an exception.

One might question whether the three investigators also have procurement related conflicts of interest. Most institutions of higher education have a vendor policy that requires any university employee who has a financial interest in a commercial vendor to disclose that interest. This disclosure leads to a review of the conditions of the purchase, to determine whether the employee is in a position to influence the purchasing decision and thereby enhance his or her financial interest. The Committee could find that in this case there is no procurement related conflict since the company is described as the only reputable vendor of the NAC.

D. Risk-benefit analysis:

Where institutional policies might allow this research to be conducted under certain circumstances, what are the risks of this arrangement?

1. *Is there an increased risk to human subject safety? Is there an increased risk of failure to adhere to the inclusion/exclusion criteria of the protocol? Is there a danger of over-stating the potential benefits of the drug while soliciting consent?*
Yes, there is increased risk to the safety of research participants. The judgment of Drs. Weiss and Gruen in the selection, recruitment, and consent process and in the clinical assessment of the human participants could be influenced by their expectation of potential royalties if the outcome favors this use of NAC.
2. *Is there a risk to data integrity?*
Yes. Dr. Jones in particular could be influenced in his analysis of the data by his financial interests. Drs. Weiss and Gruen could be influenced in how they record their clinical assessments. The risks are much reduced, though, by the fact that the study is double-blinded and placebo-controlled.
3. *Is there a risk of an appearance of a conflict of interest?*
Yes. Both the public and the CF patients expect their physicians and the scientists who analyze the data to be free from the potential for compromising the integrity of the data and the safety of the human subjects. The risk here is magnified by the fact that all three investigators have financial interests in the outcome of the trial.
4. *Could the outcome of the study benefit the public?*
Yes. Lung inflammation is a serious consequence of CF that complicates the disease. Alleviation of this complication for CF patients would measurably improve their health and quality of life.

E. Could Drs. Weiss, Gruen, and Jones be allowed to pursue this research proposal in light of their COIs?

All three individuals should first be asked to reduce or eliminate their financial interests. The AAMC guidelines recommend that conflicted investigators who do not divest should not conduct clinical research unless they can justify an exception to the “rebuttable presumption” test. What speaks against Drs. Weiss and Gruen is that they do not appear to be uniquely qualified to conduct the trial, even though it does require clinical specialization and expertise in the treatment of CF patients. However, since University is likely to have only one or two CF specialists with the requisite patient population for this trial, the Committee could find compelling reasons to allow them to participate, especially in view of their collaboration with Dr. Jones. The Committee could find that Dr. Jones is uniquely qualified because his laboratory has the special method for analyzing the glutathione levels in neutrophils. The combination of these various circumstances could present compelling circumstances for allowing the trial to be conducted at University. There is also a compelling reason to use NAC from this company, because it is not otherwise available for the study.

If the arrangement is not prohibited by University’s policy, the Committee could consider whether a management plan would allow the research to proceed. In that case the institution could consider imposing one or more of the following management conditions:

1. At a minimum, require all three investigators to fully disclose all their financial interests in all relevant publications, presentations, and consent forms and to provide this information also to individuals on the study team.
2. If only Drs. Weiss and Gruen are considered uniquely qualified to select and recruit human subjects, require an unconflicted person, who does not report to them, to obtain the consents from research participants.
3. Require the formation of an oversight committee to address the integrity the recruitment, selection and consent process, to evaluate the raw data, and to review manuscripts. The Committee could ask the division director to share some responsibility for ensuring the responsible and ethical conduct of this research.

4. Require the hospital pharmacy to “blind” the drug/placebo for administration to the patients and to maintain the code until the study is complete.
5. Require all flow cytometry and other research trial data from Dr. Jones’ laboratory to be stored immediately after collection in a secured form that would protect against any attempted editing unless or until the code is released.
6. After the treatment phase of the trial is complete, require preliminary data analysis to be carried out with the investigators remaining “blind” to patient treatment assignment groups.
7. After preliminary analysis have been completed, require a statistician independent of Drs. Jones, Weiss, and Gruen to “break” the code and analyze the trial. The statistician’s analysis will have to be based on predetermined endpoints and outcome measures and will determine whether the trial arms differ significantly for the trial endpoints.

Case 6: Licensed Intellectual Property, and Ownership of Equity in a Start-up Company

A. Description of the research:

Dr. Lief, Professor of Human Genetics and Medicine at University, is an expert in cancer research. From his animal studies, he has developed an infectivity-enhanced adenovirus to be a new vector for gene therapy for various types of cancers (the IP). This breakthrough has been recognized as valuable intellectual property and University’s Research Foundation has licensed it to Dr. Lief’s start-up company. Dr. Martin, another faculty member in the same department who is independent of Dr. Lief, proposes to be the principal investigator on a University based Phase I safety trial in women with recurrent ovarian carcinoma using Dr. Lief’s vector to deliver the gene therapy.

The aims of the trial are to test (a) the maximum tolerated dose, spectrum of toxicities, and potential anti-tumor clinical activity encountered with IP delivery; (b) the biologic effects encountered with IP delivery; and (c) the immunologic response generated against the IP. Dr. Lief’s company plans to sponsor the research by issuing a grant to Dr. Martin. Dr. Martin in turn proposes to subcontract the assay analysis to Dr. Lief’s laboratory at University, and Dr. Lief proposes to serve as principal investigator for this subcontract. He will devote 5% effort on this project; however, he is not going to charge his salary to the grant because that would consume a significant portion of the available funding; instead, the University department in which both faculty members are employed would have to cost-share his effort on the project. Dr. Lief’s postdoctoral fellow will be reimbursed for 85% effort and his research specialist for 50% effort on the grant.

B. Description of external interests and university roles:

When the patent for the invention was filed by the University Research Foundation, Dr. Lief, his spouse and several colleagues in his department were listed as inventors. Dr. Martin is not listed as one of the inventors nor does he have any affiliation with the start-up company to which the invention was licensed.

The company which Dr. Lief formed is in its early start-up phase. When it was established, a CEO from the outside was hired. However, Dr. Lief is the Vice President for Scientific Affairs and his spouse is the Treasurer of the company. They do not have any laboratory space, but Dr. Lief and his spouse have a home office in their basement. Dr. Lief, his spouse, a number of colleagues, and the University Research Foundation hold equity in the start-up. Dr. Lief, his spouse, colleagues, his department and the University Research Foundation will also receive fees and royalties through the distribution schedule included in the license agreement. Dr. Lief holds a senior faculty position with the university but his spouse has no association with it. Colleagues holding equity in the start-up company have faculty positions in the same department as Dr. Lief but are not involved with the research or the human subjects. The department chair has no association with the company, but the department would benefit from the distribution of royalties under University’s policy.

C. Does a specific conflict of interest exist?

Yes, there are conflicts at several levels. AAMC guidelines and the policies of many institutions of higher education define equity in a start-up company and the potential receipt of royalties from licensed intellectual property as significant financial interests that could influence an investigator's judgment in carrying out research. Dr. Lief has a conflict of interest, since he has founder's equity in the start-up company that now proposes to sponsor clinical research to be conducted by Dr. Martin and subcontracted to Dr. Lief.

The University/University Research Foundation's equity and the chairman's share in the potential future royalties constitute institutional conflicts of interest that could be a reason not to conduct the research at University. Both Dr. Lief and University would benefit from the royalty share if the research outcomes favor Dr. Lief's gene therapy vector. Dr. Lief's conflict is aggravated by his conflicting fiduciary duties to both University and his company, in which he and his spouse are officers. The conflict would not be eliminated even if he stepped down from his position as an officer of the company, since conflict of interest regulations include spouses in their definition of key personnel. Dr. Martin does not have a personal conflict of interest.

D. Risk-benefit analysis:

Where institutional policies might allow this research to be conducted under certain circumstances, what are the risks of this arrangement?

1. *Is there an increased risk to human subject safety? Is there an increased risk of failure to adhere to the inclusion/exclusion criteria of the protocol? Is there a danger of over-stating the potential benefits of the drug while soliciting consent?*
No. Dr. Martin has no financial interest that would influence her judgment in conducting her part of the trial.

2. *Is there a risk to data integrity?*
Yes, since all the assays would be done under a subcontract by Dr. Lief, whose equity in the sponsoring company and expectation of future royalties from sales could influence his conduct of the assays and his collection and interpretation of the data.

3. *Is there a risk of an appearance of a conflict of interest?*
Yes, and the risk is high. The institutional COI probably cannot be managed in this case, in view of the negative publicity likely to surround gene therapy trials when the institution and/or the investigator are conflicted.

4. *Could the outcome of the study benefit the public?*
Yes. Thousands of women are newly diagnosed with ovarian cancer and thousands more die annually. Because screening strategies are ineffective and symptoms are vague, the ovarian cancer is already advanced in a large percentage of affected women at the time of initial diagnosis. The human subjects in this proposed study all have recurrent cancer that is unresponsive to the treatments available at this time. The new treatment may result in significant tumor shrinkage or stabilization and prolongation of life without undue risk of serious toxicity. The study could also lead to improved virotherapy approaches to this disease and could significantly influence the development of gene therapy strategies for a variety of other diseases.

E. Could the investigators be allowed to pursue this research proposal in light of their and University's conflicts of interest?

AAMC guidelines and most institutional policies would prohibit Dr. Lief from participating in the trial. His financial interests cannot effectively be managed, and the facts do not support an exception to the "rebuttable presumption" test.

University could eliminate the institutional conflict by divesting its equity in the sponsoring start-up company. If another laboratory, independent of Dr. Lief could be identified to conduct the assays, Dr. Martin would be able to conduct the trial at University without any conflict of interest. She should, however, be careful not to consult with him regarding any aspects of the trial and should not discuss the results of the trial with Dr. Lief prior to publication.

Provided that Dr. Lief's participation in the trial as a subcontractor is not allowed, related conflict issues will be moot. Otherwise, one issue would have involved the inappropriate involvement of his staff and students; another one might focus on his plan to have the department cost-share his salary. Asking University to pay for his effort to be expended on behalf of the company would have constituted a serious breach of fiduciary duty to his employer.

Case 7: Part A: Administrative Conflict, Equity in Start-Up Company, and Intellectual Property

A. Description of the research:

Dr. Wilson, Chair of the Department of Neurology at University has developed a new drug that promises to slow the development of Alzheimer's substantially in patients diagnosed in the early stages of the disease. This drug was developed in her laboratory in collaboration with Dr. Weiss, a non-tenured assistant professor in the department. Animal studies in her laboratory have been extremely promising, and in compliance with University policy, Dr. Wilson seeks approval to form a start-up company that will sponsor Phase 0, I, and randomized Phase II clinical trials in which she will be the principal investigator and Dr. Weiss will be co-PI.

Dr. Wilson proposes that University will license the new drug to the start-up company in which she will be President and CEO with Dr. Weiss as Vice President for Research. She plans to negotiate the license on behalf of the company, because she states that there are no others who could do so and because the company has no funds to hire an attorney or CEO. She will seek venture capital for the company, realizing that when that is accomplished, her own equity ownership will be reduced and a new CEO will be hired. At that time she plans to assume the function of Chair of the Board of Directors and Chair of the Scientific Advisory Board.

B. Description of the external interests:

Dr. Wilson proposes that she will own 80% of the equity in the start-up company initially and that the University and Dr. Weiss each will own 10% equity. Dr. Wilson will also be paid \$40,000 annually for her duties as Chair of the Board and Chair of the Scientific Advisory Committee. The terms of the license include royalty payments once the drug is successfully marketed. According to University policy, this revenue will be distributed to Drs. Wilson and Weiss privately, to their university research accounts, to their department, to the medical school, and to the University. At the time of the proposal, venture capital has not yet been secured and the start-up company's value is not easily assessed.

C. Does a specific conflict of interest exist?

Yes. There are administrative and financial factors that could significantly influence the conduct of the proposed research, presenting risks to the participating human subjects, to the investigators and to the University.

As department chair, Dr. Wilson is an officer of the University with authority to make decisions about the future of Dr. Weiss. She has the authority to recommend Dr. Weiss' annual salary, to allocate departmental space and resources for his research needs, and to assign his teaching duties. She can even influence his promotion and tenure. As department chair, Dr. Wilson is also in a position to allocate space and resources to her own research projects. Without further analysis of the potential risks to human safety and integrity of research data, most institutions would conclude that an administrative institutional COI exists.

In view of her administrative role in the University, Dr. Wilson's proposed role in the company could greatly distort her primary commitments to the institution and to her colleagues. University officers have a fiduciary duty to act in the best interests of the institution but under state and in some circumstances federal law, officers of companies also have a fiduciary duty to act in the best interests of the company.

Many institutions would not allow their faculty to serve as officers and board members in companies that sponsor their research, particularly when the faculty member is an officer of the University. Even if she were not department chair, her institution might conclude that her fiduciary duty to the institution precludes her from serving as an officer or board member in the company sponsoring her research. Many universities have policies to this effect.

In addition, PHS regulations and AAMC and AAU guidelines identify certain relationships with an external research sponsor that have the potential to influence the research outcome in favor of the financial interests. These include compensated services, such as paid membership on the Scientific Advisory Board, a management position in the company such as an officer or board member, equity, and royalties.

Institutional and administrative conflicts aside, both Dr. Wilson and Dr. Weiss would have individual conflicts of interest, since both propose to have financial interests in the company that might influence their judgment in designing the research protocols, selecting and recruiting the human subjects, collecting and analyzing the data, and publishing the results.

D. Risk-benefit analysis:

Where institutional policies might allow this research to be conducted under certain circumstances, what are the risks of this arrangement?

1. *Is there an increased risk to human subject safety? Is there an increased risk of failure to adhere to the inclusion/exclusion criteria of the protocol? Is there a danger of over-stating the potential benefits of the drug while soliciting consent?*
Yes, both Dr. Wilson and Dr. Weiss stand to benefit from equity in the company and from potential royalties if they select human subjects, administer the experimental drug, or explain the risks to the human subjects in ways that favorably influence the outcome of the research. There might also be an institutional conflict of interest. Arguably the University's equity ownership could influence its oversight of the research, although this risk may be more apparent than actual, because individuals who handle decisions about the University's investments are usually not in close contact with research administration, the IRB, and the investigators. Universities should take note that institutional conflicts become more difficult to manage if those who oversee research administration in the University also oversee technology transfer and make decisions about companies in which the University invests.
2. *Is there a risk that the financial interests of Drs. Wilson and Weiss could cause them to compromise the integrity of the data?*
Yes. Their conflicts could influence not only how they design and conduct the protocol, but also how they collect the data, analyze and report them.
3. *Is there a risk of the appearance of a conflict of interest?*
Yes. If both the University and the investigators have substantial financial interests, the appearance of a COI may persist even if the conflict is managed, and this could affect the reputations of both the individual investigators and the University. For example, the Committee might consider assigning oversight of Dr. Weiss' faculty development and decisions about his salary, promotion, and resources to another department chair. However, this strategy would be unlikely to erase from the minds of other departmental faculty members and the public the perception that, very possibly, Dr. Wilson could still influence Dr. Weiss' academic career and the research outcomes in positive or negative ways.
4. *Could the outcome of the study benefit the public?*
The drug has the potential to give extended quality of life to Alzheimer's patients. This would be an immense benefit to these patients and their families, and could constitute economic and intellectual savings for the public. However, without divestiture or conflict management, the research on the validity of the drug as a treatment will be in question.

E. Should Drs. Wilson and Weiss be allowed to conduct clinical trials sponsored by the company?

The University should seek an external valuation of the technology and an expert opinion on whether the license should be pursued with the start-up or another company. Using the results of these assessments as a basis for the negotiation, and in consideration of national standards and institutional policies regarding equity, the University will be able to negotiate for itself and allow Dr. Wilson to participate in the negotiation. The preferred route, however, is for the company to have a separate CEO or attorney with whom the University would agree on the license terms rather than Dr. Wilson signing on behalf of her company. In any case, when universities take equity in companies that propose to sponsor research at the institution, they create a conflict of interest that will be difficult to manage in the future.

Most universities would not allow Dr. Wilson to serve as an officer or board member in the company if the company plans to sponsor research conducted by Dr. Wilson. She would have to take steps to distance herself from the management of the company. Further, most Universities would not allow the start-up company to be formed or the research to go forward as long as Dr. Wilson is department chair and thereby in control of her collaborator Dr. Weiss.

Although Dr. Weiss has no administrative conflicts, his equity in the start-up and potential royalties could seriously bias his judgment in the conduct and interpretation of the research.

These conflicts are so unmanageable that neither the formation of the start-up company nor the University's and investigators' participation in the proposed clinical trials should be allowed. Theoretically Drs. Wilson and Weiss could divest themselves of their financial interests in the start-up company, but this is not a realistic solution, since neither would be likely to engage in the effort without compensation.

The research could be sponsored at another institution, in which case the University could hold equity in the company. Alternately, the research could be conducted at the University by different investigators. The management plan might then include the following provisions:

1. Require that the new investigators be independent of Drs. Wilson and Weiss.
2. Stipulate that Drs. Wilson and Weiss may not hold management positions in the company as officers, board members, or chair of the scientific advisory committee, but that they could serve as consultants on the trial or members of the scientific advisory board. The commitment of effort of each must remain within allowable limits.
3. Allow Dr. Wilson to negotiate the license terms with the University, since no one else with comparable scientific qualifications is available. Care should be taken to ensure that in the negotiation of the business terms the University is not perceived as taking an unfair advantage in its position as employer of the two faculty members. However, the preferred strategy is to avoid such potential conflicts by dealing with an attorney acting on behalf of the company.
4. Permit Drs. Wilson and Weiss to request limited participation in the clinical trials. If their request is granted, it should not include contact with human subjects, or collection of data.
5. Determine that the analysis of data remains subject to review by unbiased experts. If it were necessary or advisable to involve Drs. Wilson and Weiss as consultants, they should be required to make full disclosure of their peripheral involvement, of the role of their company, and of their potential royalties. This disclosure must be shared with the participating human subjects, and full disclosure must also be provided in all forms of publication involving the clinical trial.
6. Make Drs. Wilson and Weiss aware that their company ownership and positions as consultants will affect how they conduct future research related to this drug at the University. They will have a conflict of interest for example, if they apply for an NIH grant to further develop the technology, perhaps to develop a drug to prevent or cure Alzheimer's or to prolong the delay in the onset of symptoms. This conflict will require careful and stringent scrutiny, and the University may be exposed to charges of "pipelining" if new research projects are directed to the Wilson-Weiss company.

Case 7: Part B:

Dr. Wilson developed the technology alone. Initially she proposes that the University will own 20% and she will own 80% of the equity in the start-up company. Her equity ownership will be reduced to approximately 20-30% with venture capitalist investment. All other facts are the same.

A. Does a specific conflict of interest exist?

Yes. The possible distortion of the research due to financial conflicts is increased, since Dr. Wilson's equity share in the start-up and her expected royalty revenue from sales will be larger without Dr. Weiss joining the company.

Potential conflicts due to a violation of fiduciary responsibilities are not eliminated. As stated in the alternate version of this case, many institutions would not allow their faculty to serve as officers and board members in companies that sponsor their research. As a faculty member Dr. Wilson could easily find herself in an adversarial position to the University or the company, and most institutions would conclude that this conflict of interest is unmanageable.

B. Could Dr. Wilson be allowed to conduct clinical trials sponsored by the company?

This might be possible provided University decided to take no equity. In that case, the Committee would weigh the benefits and risks of two faculty members who wish to start up a company, hold equity and potentially receive royalties, and conduct clinical trials sponsored by the company. Applying the rebuttable presumption guideline reveals however that Drs. Wilson and Weiss are not uniquely qualified to administer the drug and observe its results in Alzheimer's patients and the institution is not uniquely qualified as the only site where the trial could be conducted. Accordingly, the presumption against their conduct of the clinical trial is not likely to be overcome. The research could be sponsored at another institution in which case the University could hold equity in it.

Case 8: Controversial Funding Source and Purpose of Research

A. Description of the research:

Dr. Cho, Professor of Radiology in the Medical School at University, is an expert in functional magnetic resonance imaging (fMRI). He enjoys a national reputation for his work on mapping parts of the brain that "light up" during various day-to-day activities, whenever people make choices about what to eat, wear, or do. Dr. Cho correlates his findings with the studies of others regarding certain activities and respective positive or negative emotions with which the parts of the brain are associated. Over the years he has built a body of evidence showing that under certain circumstances, knowing which parts of the brain "light up" can allow predictions about the choices an individual will make.

Dr. Cho is approached by a well-known soap company that proposes to sponsor a human subjects research study at the medical school with Dr. Cho as the PI. In the study he will ask human subjects questions about the soap product and about different advertising strategies in order to determine what appeals to them. The company will use the results for improving its marketing campaign and demands exclusive rights to the results of the study. Dr. Cho has already made it clear that neither he nor the University will allow this restriction on freedom of publication.

Dr. Cho proposes to use the medical school's MRI equipment and offers to reimburse University with part of the research funds provided by the soap company. In his proposal, he takes the position that the study will allow him to test new aspects of choice, and that this research is valid regardless of how the results of the study will be used. In his view the study is not substantially different from a drug trial, where the sponsoring drug company hopes eventually to market the drug.

B. Description of external interests:

Dr. Cho has no financial relationship with the soap company. No patentable technology is expected to result. The soap company is not a vendor to the University, and the University and its officers have no investments in the company.

C. Does a specific conflict of interest exist?

There is no financial COI under the AAMC and AAU guidelines or the PHS regulations. A COI Committee could decide that it has no jurisdiction, and that the University should use other more appropriate venues for considering the questions that arise in connection with this proposed project.

At issue is whether the project constitutes valid research in keeping with the missions of the University or whether it is a marketing service in which the soap company wants to engage the university. Clarification about the extent of a potential COI might be achieved by asking questions such as: Are basic academic values upheld? Is the research appropriate to the mission of the institution? Are uses of institutional resources and facilities appropriate? If the project is defined as a marketing service, the COI Committee could conclude that a conflict of interest with the missions of the investigator and University does exist and that pursuing it would place the reputations of the University and the investigator at risk. The Committee should also consider whether denying the project abridges Dr. Cho's academic freedom; whether the University's equipment, purchased for patient care and research, can be used for the marketing service; and further, whether such service is in keeping with the University's not-for-profit tax status.

Several different outcomes are possible. The Committee could conclude that Dr. Cho's proposed study should be categorized as human subjects research because he proposes to evaluate human behavior by testing choices that have not been tested in other relevant studies and because he has a considerable record of published results. In that case, the study could go forward. On the other hand, the Committee could conclude that the sponsor's reason for the study and its planned use in marketing define it as a marketing study. The comparison to a drug study may be considered irrelevant, since drug study results are not directed primarily at marketing but rather at finding treatments for disease, even if the company might eventually sell the drug based on the results. In that case, the study will be denied. Finally, the Committee could conclude that even though the study could be defined as appropriate research, the controversial funding source and intent constitute a major conflict of interest with the University's missions. In this case, a risk-benefit analysis could be useful to determine whether the study should be allowed.

D. Risk-benefit analysis:

Where institutional policies might allow this research to be conducted under certain circumstances, what are the risks of this arrangement?

1. *Is there an increased risk to human subject safety? Is there an increased risk of failure to adhere to the inclusion/exclusion criteria of the protocol? Is there a danger of over-stating the potential benefits of the drug while soliciting consent?*
Since the study is not invasive, there are no immediate concerns for the physical safety of human research participants.
2. *Is there a risk to data integrity?*
The possible conflict with the missions of the University is not likely to influence the judgment of Dr. Cho in conducting or publishing the study.
3. *Is there a risk of an appearance of a conflict of interest?*
There would be no appearance of a financial COI, since neither the University nor Dr. Cho would benefit financially. However, there is a high risk that the public could construe the activity as a conflict with what the University should be doing and even if it is arguably research, whether it is research worth engaging in. There is also a risk that the reputations of Dr. Cho and the University could be challenged, even if there is no financial COI, since University equipment purchased for patient care and research would be used for the study. The University might have difficulty defending this equipment use publicly.
4. *Could the outcome of the study benefit the public?*
Further insight into brain function might be a benefit to medicine and science, though Dr. Cho could possibly address the scientific questions more effectively in another of his studies funded by a different source.

E. Should the study be allowed to take place at the institution?

Institutions will differ in their conclusions about whether the benefits outweigh the risks and where to draw the line in defining what differentiates appropriate research at an institution from marketing services for hire. Dr. Cho is not specifically conflicted in being the PI and there is no particular management concern that might require specific disclosures in resulting publications.

Case 9: License, Consulting, and Equity in Start-up Company

A. Description of the research and role of the researchers in the University:

Drs. Jefferson and Suarez, tenured Professors of Neurosurgery, at University, have invented an implantable wafer containing chemotherapeutic agents believed to be active in treating brain tumors. Based on their animal studies, they hypothesize that slow release of chemotherapy at the tumor site will extend the life of patients, whose life expectancy is typically six months from diagnosis. Drs. Jefferson and Suarez propose to be co-PIs of a Phase I safety study of the wafer in a group of ten patients. NeuroX, a company that has obtained a license from University for use of the wafer, will sponsor the Phase I study.

B. Description of the external interests:

NeuroX is an early-stage biotechnology company, founded by Dr. Jefferson with the University's approval. The terms of the license agreement include modest up-front fee payments, 3% royalty on sales, 10% royalty on sales by sub-licensees, and a 10% equity stake in NeuroX to the inventors. Under the University's intellectual property policy, Drs. Jefferson and Suarez would personally receive and split 40% of the proceeds from sale of the University's stock; and their labs would split 30% of the proceeds. The same distribution schedule also would apply to fees and royalties.

However, at the time of the licensing event, Dr. Jefferson bought out all the future financial interests of Dr. Suarez in the implantable wafer for a large lump sum payment under an agreement fully disclosed to the University. He is the only University faculty member who now holds financial interests in NeuroX and the implantable wafer. The investors in NeuroX have offered Dr. Jefferson an additional 10% equity position, and they want him to serve as chair of the company's scientific advisory board, with compensation of \$50,000 per year.

C. Does a specific conflict of interest exist?

Dr. Suarez has no financial interest in the proposed project. Dr. Jefferson's financial interests substantially exceed the thresholds permitted under policies recommended by AAMC, AAU, PHS, and University. Therefore the COI Committee could conclude that Dr. Jefferson may not participate in the study unless he can rebut the presumption against his participation in the research. Dr. Jefferson argues that as a highly-skilled brain surgeon and the co-inventor of the wafer, he is uniquely qualified to conduct the study. He has told the Committee that he does not intend to participate in larger-scale clinical studies; however, he states that his surgical expertise is needed in the Phase I study to fine-tune the wafer placement procedure. He and Dr. Suarez optimized the procedure in animal studies, but it must be perfected in humans. He also states he would welcome oversight of his data collection and analysis procedures.

D. Risk-benefit analysis:

Where institutional policies might allow this research to be conducted under certain circumstances, what are the risks of this arrangement?

1. *Is there an increased risk to human subject safety? Is there an increased risk of failure to adhere to the inclusion/exclusion criteria of the protocol? Is there a danger of over-stating the potential benefits of the drug while soliciting consent?*
Under the study protocol, the wafer will be implanted during the course of clinically indicated brain surgery. However, in addition to removing the tumor, Dr. Jefferson or Dr. Suarez will implant the wafer. The key study endpoint is survival. Dr. Jefferson is likely to recruit from his own patients, and his influence over his patients is substantial. They may believe that his advice is sound and that there is little or minimal risk despite disclosures about the experimental nature of the implant. Some research has shown that a physician's financial interest in a product increases patients' trust or belief in the efficacy of the product. In light of Dr. Jefferson's significant financial interest, there is a risk of bias in recruiting and obtaining subjects consent. However, Dr. Jefferson states that he is willing to hand off the human subject recruitment and consent process to Dr. Suarez, who has no remaining financial conflict of interest.

2. *Is there a risk that Dr. Jefferson could compromise the integrity of the data to favor his financial interests?*
Data will be collected and analyzed by the Jefferson-Suarez research team. Any bias in the study design or data analysis probably will be difficult to discern, since there are no built-in safeguards such as those provided by a Data Safety Monitoring Board (DSMB), a coordinating center that analyzes the data and confirms their validity by correlation with data from other sites. The risk is high for the potential benefit of over-stating results, towards enhancement of NeuroX's value. The company would thus appear to be a more attractive investment for angel investors or venture capitalists or as a target for acquisition.
3. *Is there a risk of an appearance of a conflict of interest?*
For Dr. Jefferson there is a significant appearance of a conflict of interest since he co-invented the wafer and has substantial financial interests in the success of the treatment. Dr. Jefferson and the institution would have reputational risks if the study were allowed to go forward as proposed. Dr. Suarez has an intellectual investment in the wafer, but the presumption is that peer review processes will neutralize this type of interest, as effectively as in other published research in which the investigator has no direct financial interest in the outcome.
4. *Could the outcome of the study benefit the public?*
If successful, the study could have tremendous medical benefits.

E. Should Drs. Jefferson and Suarez be allowed to conduct clinical trials sponsored by the company?

The Committee must evaluate this case in light of the institution's COI policy; the risks of a "managed" COI; and the potential benefits of permitting Dr. Jefferson to participate in the study. The Committee might conclude that the benefits to the public can be obtained without the risk of having Dr. Jefferson involved as a participant in the study since Dr. Suarez has equal experience and expertise.

If the COI policy categorically prohibits participation of a conflicted investigator, Dr. Jefferson will either have to forego the study or reduce his financial interests to an acceptable level before proceeding. If the COI policy prohibits the arrangement, but allows for limited exceptions, the COI committee must first determine whether an exception is warranted.

This would be a single-center study that is partly under the control of a conflicted investigator. Even with a management plan that mandates disclosure of interests, restriction of Dr. Jefferson's ability to consent subjects, and oversight over data collection and analysis, any bad outcome attributed to the clinical research would lead to questions, criticism, or potential litigation because of the conflict of interest. In approving a "managed" COI, the institution would be taking a calculated risk.

The COI Committee could find that Dr. Jefferson has not successfully rebutted the presumption barring his participation. The evidence about his unique qualification to participate as a surgeon in the study may not be convincing, since Dr. Suarez and he co-invented the implantable wafer and jointly conducted the preliminary animal studies and surgeries. In that case, only Dr. Suarez would be allowed to conduct the study.

If Dr. Jefferson presented additional convincing evidence that his participation is essential for the trial to occur, the COI Committee should impose stringent management that might include:

1. Require Dr. Jefferson to disclose his own (and the institution's) financial interests on consent forms and to prospective subjects; to other members of the study team and to any collaborators; both in oral presentations and written publications.
2. Allow only Dr. Suarez or another designated individual who does not report to Dr. Jones to solicit and obtain consent. Dr. Jones may explain the study procedures to subjects, but he should be excluded from the recruitment and consenting process.

3. Appoint one or more knowledgeable, disinterested individual(s) to oversee data collection and analysis, because of the close relationship between Drs. Jefferson and Suarez. At a minimum, require an independent expert to review the manuscript and have access to the raw data if needed.
4. Allow Dr. Jefferson a co-investigator role, with the majority of the responsibility for the study resting with Dr. Suarez. Dr. Suarez and possibly an independent reviewer should assure the COI Committee that the design of the study is valid, since it was designed by Dr. Jefferson.
5. Require Dr. Jefferson to reduce his consulting fee paid by the company to a level below the threshold of the institutional policy and below \$10,000. He should relinquish his position as chair the scientific advisory board but may continue to serve as one of its members.

Case 10: Equity in Company, Research for a Competing Company

A. Description of the research and role of the researcher in the University:

Dr. Bagli is Associate Professor of Orthopedic Surgery in the Medical School at University. She has invested in equity in Curvno, an early stage company that has grown and now sells a few highly specialized but heavily used surgical spine devices. She has carefully avoided involvement in the medical school's purchasing process. Insertco, a competing company, contacted Dr. Bagli about serving as the PI in a phase II clinical trial of its newly developed device that will compete on the market with Curvno's most profitable device. Dr. Bagli has submitted the proposal for University review.

B. Description of the external interests:

Dr. Bagli's equity in Curvno is almost 15%, in excess of the threshold under University COI policy.

C. Does a specific conflict of interest exist?

Yes. Dr. Bagli's financial interests in Curvno could be either favorably or adversely affected depending on the outcome of the clinical trial and subsequent marketing of the competing spine device.

D. Risk-benefit analysis:

1. *Is there an increased risk to human subject safety? Is there an increased risk of failure to adhere to the inclusion/exclusion criteria of the protocol? Is there a danger of over-stating the potential benefits of the drug while soliciting consent?*
There is a risk that Dr. Bagli could recruit patients who might receive less benefit from the surgical device or that she could overplay the risks with some patients to try to jeopardize the successful outcome of the trial.
2. *Is there a risk to data integrity?*
Yes, there is a risk that Dr. Bagli could compromise the integrity of the data to achieve an unfavorable outcome in the test of the competing device and thereby protect her financial interest in Curvno. This could occur at the level of implantation, collection of data on the outcomes, analysis, and interpretation of the data, and drafting of the manuscript. Of course, her reputation would be on the line if trials conducted at other sites refuted her biased report of the outcome.
3. *Is there an appearance of a conflict of interest?*
Yes, there is both a real and an apparent conflict. Dr. Bagli could also be seen as influencing decisions regarding stock trading. There is also a risk of reputational damage to Dr. Bagli and to the University.
4. *Could the outcome of the study benefit the public?*
It is not clear whether the new device would be a substantial improvement over the one currently on the market. The question before the committee is whether the benefits to medicine, science, and public health will result if the research is allowed.

E. Should Dr. Bagli be allowed to be the principal investigator in the study?

Without elimination of the conflict or a management plan, the study should not proceed with Dr. Bagli as the PI. A COI Committee could conclude that Dr. Bagli has not presented evidence to overcome the rebuttable presumption that she should not be allowed to participate in the trial. Indeed, there appears to be no compelling reason for Dr. Bagli to be involved in the trial at all. The Committee could propose that Dr. Bagli could sell her equity in Curvno to eliminate the conflict of interest, a step that would then make it possible for her to conduct the trial. Alternatively, Dr. Bagli might present compelling evidence that her involvement in the trial is essential, perhaps because only she has a sufficient patient population for recruitment of a sufficient number of patients. In that case, a management plan would have to be agreed to with the following elements:

1. It should be mandatory for Dr. Bagli to make full disclosure of her financial interests in a competitor company to other participants on the research team, students and trainees, human research subjects, the academic supervisor, peers, and the public in all forms of presentation and publication.
2. The protocol should designate as PI another surgeon, competent in use of the spinal devices, who is independent of Dr. Bagli. Dr. Bagli would function as co-PI with limited responsibilities in the study.
3. Dr. Bagli would be excluded from obtaining consent from the patients. Any patients she recruits to the study must be reviewed by the new PI to ensure that all meet the proper eligibility requirements.
4. Collection of outcome data should be the sole responsibility of the PI and not of Dr. Bagli, as should be the analysis and interpretation of the data. If Dr. Bagli is involved in analysis of the data and preparation of the manuscript, an unbiased expert should review the manuscript and have access to the raw data to confirm the report.
5. If possible, steps should be included in the protocol to blind the data from both Dr. Bagli and the new PI initially.
6. Residents and fellows that work with Dr. Bagli should be prohibited from participation in the research protocol, unless their participation can be overseen by the unconflicted PI.

APPENDIX C

Definition of Financial Interests in Research

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:

1. 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);
2. Equity interests, including stock options, in a non-publicly-traded financially interested company (or entitlement to the same);
3. Equity interests (or entitlement to the same) in a publicly-traded financially interested company (see exceptions below);
4. 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;
5. 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;
6. 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:

1. Interests of any amount in publicly traded, diversified mutual funds.
2. 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.
3. Salary and other payments for services from the institution.

APPENDIX D

Institutional Policies and Practices on Consulting: Topics and Questions to Consider

[Note: These points to consider were compiled based on an examination of consulting policies of several institutions. The list is neither exhaustive nor exemplary. It represents an aggregation of topics addressed in one or more of the policies examined.]

1. Express linkages to conflicts of interest policy; when does consulting present a potential conflict of interest and how will that trigger be identified?
2. Establishment of time allowed
 - a. 1/7 days
 - b. 20%
 - c. 1/5 days
 - d. 13 days per quarter
 - e. No specification
3. Specific prohibitions?
 - a. Speakers' bureaus
 - b. Outside medical practice
 - c. Other academic appointments
 - d. Acting as an employee of the university
 - e. Other?
4. Attention to specific types of activities
 - a. Speakers' bureaus or speaking engagements whose primary purpose is product marketing rather than an independent presentation of educational material
 - b. Service as an officer, director, member of the scientific advisory board of a company
 - c. Service as an expert witness
 - d. Acting as an employee of the institution/acting as a private agent or employee of an outside entity
5. Attention to particular terms in consulting agreements
 - a. Intellectual property and compliance with university intellectual property policies
 - b. Duty to publish and prevention of publication restrictions
 - c. Non-competition provisions that may affect academic research
 - d. Confidentiality
 - e. Scope of work
 - f. Stated or implied use of institutional resources
6. Is disclosure required of intent to engage in consulting?
 - a. From whom: Full time faculty, part time faculty, volunteer faculty, students, trainees, staff

7. What must be disclosed?
 - a. Agreement
 - b. Summary of terms of agreement
 - c. Scope of work
 - d. Compensation in whatever form
8. When must disclosures be made?
 - a. Annually
 - b. As external commitments are proposed
 - c. Only if compensation exceeds a stated threshold
 - d. Only if external activity relates to university duties
9. Who review/approves disclosures?
 - a. Is review required?
 - b. Is approval required?
 - c. What institutional official reviews/approves?
10. What is the process for disclosure/review/approval?
 - a. Prior completion of tutorial about consulting?
 - b. On line system?
 - c. Consulting data base that is integrated with other relevant institutional data, including IRB, IACUC, IBC, and the like?
 - d. Individualized records of outside activities
11. Provisions regarding compensation received
 - a. Who gets the compensation (individual, department, institution, practice plan)?
 - b. Limits on amount of compensation that can be received?
12. Provisions relating to use of institutional personnel and resources in outside activities
 - a. Students, trainees, junior faculty
 - b. Staff
 - c. Space
 - d. Equipment
 - e. Supplies
 - f. Intellectual property

APPENDIX E

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