SHARED RESPONSIBILITY, INDIVIDUAL INTEGRITY: SCIENTISTS ADDRESSING CONFLICTS OF INTEREST IN BIOMEDICAL RESEARCH

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FASEB

The Federation of American Societies for Experimental Biology (FASEB)

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March 13, 2006

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ABOUT THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY

Founded in 1912, the Federation of the American Societies for Experimental Biology (FASEB) advances biological science through collaborative advocacy for research policies that promote scientific progress and education and lead to improvements in human health. FASEB is a federation of twenty-two not-for-profit scientific societies representing more than 80,000 research scientists, making it the largest coalition of research associations in the United States.

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PREFACE

There are many benefits to joint and synergistic relationships involving academia and industry. However, research shows that these interactions have been accompanied by serious and sometimes unaddressed conflicts or potential conflicts of interest. Responses from the media and Congress in this regard have been rapid and notable, sparking discussions about expansion of regulatory requirements and other potential burdens to investigators.

As representatives and leaders within the biomedical research community, the Federation of American Societies for Experimental Biology (FASEB) believes that maintaining the public trust and assuring the integrity of basic and clinical research is of the highest importance. Given our representation of over 84,000 practicing scientists, FASEB is uniquely positioned to proactively address these issues. While other groups have addressed conflict of interest, we are particularly concerned with the perspectives of investigators who work in the public interest in all research-based institutions, particularly academic and not-for-profit institutions where the majority of FASEB society member scientists are represented.

In July 2004, FASEB announced the intent to address conflict of interest in biomedical research, and the FASEB Board of Directors approved this initiative in December. Shortly thereafter, a steering committee was formed that developed the conference agenda and the issues to be discussed, secured speakers, and outline plans for future work from FASEB.

In June 2005, FASEB hosted the conference, "Shared responsibility, individual integrity: Scientists addressing conflicts of interest in biomedical research." The purpose of the conference was to allow investigators to consider and respond to serious challenges involving conflict of interest in biomedical research. The conference was held as part of the FASEB Board of Directors Meeting on June 14-15, 2005 in Washington, D.C. Speakers from academia, industry, government, and nonprofit associations outlined the issues. In a break-out session, groups of FASEB Board Members, society staff, speakers, and invited guests discussed issues related to four types of academia-industry relationships: research contracts, consulting and board membership, entrepreneurial activities, and training or education. The conference prepared FASEB for a continuing discussion of these issues, and a steering committee continued to develop several key issues that were raised. The FASEB Board of Directors reviewed the report in December 2005, and approved it on December 9, 2005.

This report represents a consensus statement on overarching principles and voluntary standards for the conduct and management of academia-industry interactions from the *scientists' perspective*. It is intended to be used primarily by scientists, as well as institutional leaders, policymakers, professional societies, and others. The guiding framework for this report is based on the assumption that in academia-industry relationships, there are 1) individual decisions that are made by scientists, 2) institutional, professional, and government requirements, and 3) goals and objectives that are specific to each sector. This report focuses on identifying those challenges that scientists confront in academia-industry relationships, and recommends guiding principles for these scientists that will help them appropriately secure the benefits and guard against risks of such collaborations. Although the document is generally

designed to address financial conflict of interest issues faced by individual academic scientists, some of the general principles apply to scientists broadly and address challenges that are not exclusively financial in nature. These recommended guiding principles should be used to complement, not substitute, any requirements from the government, institutions, and journals.

The vast majority of biomedical researchers are guided by the highest ethical and professional standards. Our member societies and their scientists continue to uphold practices that advance the public good. Through the leadership of the FASEB Board, FASEB member societies, their scientists, and the broader scientific and policy communities, we aim to provide scientists with better tools for navigating relationships between academia and industry in the public interest.

Leo T. Furcht, M.D.
Steering Committee Chair
FASEB President-Elect and Past Vice-President for Science Policy

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EXECUTIVE SUMMARY

Relationships between academia and industry are a fundamental part of the modern life science enterprise. It is only through such interactions that advancements in the life sciences can most rapidly achieve the maximum benefit to society. The rise in academia-industry relationships has been accompanied by increasing concerns about risks due to financial conflicts of interest. These risks include the potential to bias research, delay trainee progress, compromise efficient and wide dissemination of research results, harm human research participants, and decrease public trust in medical research.

There are several rules and policies of the federal government, institutions, professional societies, and scientific journals that guide the oversight of academia-industry relationships. To date, many of the policy recommendations addressing financial conflicts of interest have focused on the role of institutions in the review and oversight of investigators' relationships with industry,[1, 2] whereas the role of investigators has not been as well-identified. The actions of investigators as a group will determine the effectiveness of policies and practices. But in the current debate over the limits of intimacy between industry and academia, there is a clear need for voluntary standards for the conduct of academia-industry interactions from the scientists' perspective. With this goal in mind, we propose a set of guiding principles that can help investigators anticipate common challenges in industry relationships and guide their decision-making to overcome these challenges. While the document was generally designed to address financial conflicts of interest faced by individual academic scientists, some of the general principles apply to scientists broadly and address challenges that are not exclusively financial in nature.

Specific challenges for investigators discussed in this report include:

- ◊ How do investigators protect against research bias in industry relationships?
- ◊ How do investigators work with institutions to ensure requirements are fulfilled and relationships are fairly and effectively reviewed and overseen?
- ◊ How do investigators address issues of access, analysis, and dissemination of research information, data, and materials in industry relationships?
- ◊ How do investigators operate with transparency and accountability in industry consulting relationships (consulting, advisory board membership, speaker bureaus)?
- ◊ How do investigators address conflict of interest issues in their entrepreneurial activities (involvement in start-up companies and technology licensing)?
- ◊ How do investigators with industry relationships minimize the negative impacts of those relationships on training and education?
- ◊ How do investigators with industry relationships protect against risks to human research participants?

The guiding principles to aid investigators in addressing these challenges are:

- ◊ Guiding principle 1: Investigators have a responsibility and commitment to conduct scientific activities objectively and with the highest professional standards.

- ◊ Guiding principle 2: The primary responsibility of full-time investigators is to the institution. Outside activities shall complement, not compromise, institutional responsibilities.

- ◊ Guiding principle 3: It is appropriate and beneficial for academic institutions to develop and enforce their own mechanisms of review and oversight of investigator relationships with industry.

- ◊ Guiding principle 4: The academic community can and shall monitor itself through peer review of industry relationships. Institutional committees that include peer members from the same institution are appropriate and effective in reviewing disclosures of investigators' industry relationships.

- ◊ Guiding principle 5: Investigators want and need clear guidance, efficient processes, and adequate support mechanisms from their institution throughout their participation in industry relationships.

- ◊ Guiding principle 6: Investigators shall have access to, and be involved in the analysis and/or interpretation of all data generated in the research.

- ◊ Guiding principle 7: Mutual understanding of constraints, principles, and policies regarding access, analysis, and dissemination of research information, data, and materials among investigators and their students and trainees, institutions, and sponsors is beneficial.

- ◊ Guiding principle 8: Investigators shall not enter into agreements with companies that prevent publication of research results. Pre-publication review by an industry sponsor shall occur in a timely manner (no more than thirty to sixty days) so as not to unnecessarily delay study publication.

- ◊ Guiding principle 9: Investigators shall be aware of and adhere to individual journal policies on disclosure of industry relationships.

- ◊ Guiding principle 10: Consulting and advisory board relationships shall be carried out in a transparent and accountable manner and be disclosed as they are initiated.

- ◊ Guiding Principle 11: When investigators have consulting relationships with an investment firm related to their area of expertise, all parties shall be aware of the specific circumstances involved.

- ◊ Guiding principle 12: Investigators shall not use federal funds to the benefit of a company, unless this is the explicit purpose of the mechanism used to fund the research (e.g., Small Business Innovation Research and similar grants).

- ◊ Guiding principle 13: When investigators own significant equity in a company with which research is conducted, all parties shall be aware of the special circumstances involved.

- ◊ Guiding principle 14: When holding a significant role in a start-up company, investigators shall be guided by agreed-upon limits to the scope of the relationship.

- ◊ Guiding principle 15: Investigators shall be aware of and adhere to requirements of federal funding related to disclosure of inventions. Investigators shall adhere to patent law and institutional requirements.

- ◊ Guiding principle 16: Investigators shall not seek to influence their institution's technology transfer decisions for personal gain.

- ◊ Guiding principle 17: A mentor's outside commercial interests shall avoid impeding a trainee's timely progress toward his/her degree, restricting a trainee's right to publish his/her dissertation research in a timely manner, compromising a trainee's career progress, or restricting a trainee's freedom of inquiry.

- ◊ Guiding principle 18: Mentors and institutions should make trainees aware of their rights and responsibilities in industry relationships.

- ◊ Guiding principle 19: Investigators shall regard all significant financial interests in research involving human subjects as potentially problematic and thus requiring close scrutiny.

Both individuals and institutions must work together to address the conflict of interest challenges academia-industry relationships can pose. Industry and academic institutions should work together to steer investigators away from key challenges and roadblocks. But individual researchers still must diligently strive to maintain the objectivity and integrity of their investigations.[3] Integrity embodies a commitment to intellectual honesty in proposing, performing, reporting and reviewing research, and fairness in interactions with colleagues and for those an investigator has a responsibility.[4] Investigators must continue to show individual accountability in deciding to enter into relationships with industry, complying with institutional, government and journal policies, and proactively addressing conflict-of-interest challenges using these guiding principles. With careful disclosure and oversight, investigators can minimize or eliminate the risks of industry-academia collaborations and maximize the benefits to the scientific community and public. Failure to do so could have disastrous effects for the future of the scientific enterprise.

INTRODUCTION

Frequently academic scientists, administrators, and institutions carry out research for, or provide intellectual property to, industry in return for research support, honoraria, consulting fees, royalties, and equity, and other forms of compensation.[5] But the scope and nature of academia-industry collaborations have recently increased in size and complexity. This creates changes in the research environment that present both opportunities and challenges for scientists and their institutions.

SCOPE AND TYPES OF ACADEMIA-INDUSTRY RELATIONSHIPS IN SCIENCE

Relationships between academia and industry are a fundamental part of the modern life science enterprise. It is only through such relationships that the life sciences can advance most rapidly to maximize benefits to society. Collaborations between industry and academia have grown due to many factors including legislation and agency policies that encourage technology transfer and collaborative research, the increasingly complex nature of research that requires relationships across institutions and sectors, and the overall increase in the cost of doing research and development that yields therapies.

The growth of relationships between industry and academia is evident in the rise in the number of university patents[6], publications with authorship affiliations in academia and industry[7], and collaborative research agreements.[7]

Many different types of relationships exist between industry and academia, including research contracts, research grants, and consulting or licensing arrangements. Through research contracts and grants, companies provide direct support for research projects at universities. In return, companies often receive the right to license any inventions that are developed from that research. Approximately one-quarter of academic faculty members receive research funding from industry[8], representing close to $2 billion in 2004.[7]

Companies also provide direct support of academic trainees. Of 210 life science firms surveyed in 1994, 38 percent supported the education of students and fellows through grants.[9] Academic investigators also transfer their knowledge to industry via consulting and advisory board membership. Approximately 80 percent of life science companies retain academic faculty members as consultants, the most prevalent relationship.[9]

Licensing of technologies developed by academic investigators and the creation of university spin-off companies are also major types of academia-industry relationships. In FY 2004, 191 institutions reported licenses that led to the formation of 462 new companies that year.[6] Since 1980, licenses from academic institutions led to the formation of 4,543 new companies.[6]

It is important to mention that relationships exist at the institutional level as well.[10] While important, these industry relationships are not considered in this report.

BENEFITS OF ACADEMIA-INDUSTRY RELATIONSHIPS

Many important societal benefits stem from scientific collaborations between academia and industry, including translating basic scientific findings into clinical applications, and fueling local economies. Collaboration between industry and academia has led to many important therapies and research tools, such as the gene splicing technology that initiated the biotechnology industry, diagnostic tests for breast cancer and osteoporosis, and vaccines. Institutional licensing activities from FY 1998-2003 made 2,230 products commercially available, one report found.[6] Studies also reveal how academia-industry relationships make significant contributions to local economies.[11] Evidence shows academia-industry relationships are a key component of economic competitiveness and increase the future research and development spending by industry.[12]

Academic investigators also benefit by their collaborations with industry through increased access to resources to support their on-going projects. These collaborations enable academic investigators to participate in the application of their research, and it allows students and academic investigators to work on applied research projects. Studies show that industry funding correlates with increased faculty academic productivity (published articles) and commercial productivity (patents and licenses, products under review and on the market, and start-up companies).[8] Academic investigators, government researchers, and industry scientists also benefit professionally by interacting with colleagues. Such interactions facilitate the bidirectional flow of knowledge and materials. Interaction with industry provides academic investigators opportunities to participate in the application of their research, and it allows students and academic investigators to work on applied research projects. Finally, industry support may help offset wage differential between industrial and non-industrial sectors that may assist in recruitment and retention of scientists and administrators to academia.

CHALLENGES OF ACADEMIA-INDUSTRY RELATIONSHIPS AND CONFLICTS OF INTEREST

The rise in academia-industry relationships has been accompanied by increased concerns regarding conflicts of interest that are largely, but not exclusively, financial. A commonly used definition of financial conflict of interest is: a condition in which a primary interest (institutional responsibilities for research and education) is in conflict (whether real or perceived) with a secondary interest (such as financial gain).[13] A conflict of interest is a situation, and not a behavior. The presence of a conflict of interest is not necessarily an indictment of an individual, but rather an acknowledgement of a potentially challenging situation. By focusing on relationships and not conflicts of interest in this report, we hope to direct the guidance towards smart practices and other useful tools for scientists.

The most intense scrutiny of academia-industry relations focuses on risks to human research participants. High profile cases, such as the death of Jesse Gelsinger in a gene therapy trial at the University of Pennsylvania, highlight the need for protection of patients and research participants. The potential risk to human research participants has created a consensus within the medical and scientific community to increase attention to this issue.

Correlations between industry funding and published scientific conclusions that could be viewed as favorable to industry highlight the potential for relationships to introduce bias into research.[14] Do financial relationships with industry cause subtle or unconscious bias on the part of academic researchers?[15] Does industry funding affect the conduct of research or study design?[14] Will industry simply choose to have relationships with researchers that have predetermined favorable positions on their products? Or will they partner with those individuals who have the most expertise about the specific research area? The potential for bias remains an impassioned subject of discussion in the scientific community and the press.

There is also concern that deepening commercial ties can undermine academe's commitment to openness. For example, studies suggest that industry-funded results are less likely to be published or, when published, delayed even longer than the time necessary to file a patent.[8,16] Academia-industry relationships may impose other restrictions such as denial of access to research data or biomaterials to other investigators. [16, 17]

Industry relationships may impact trainees differently than principal investigators. There are concerns about specific risks, such as fewer publications or delays in publication of manuscripts and dissertations as well as constraints in the type of research that is conducted.[18, 19] From the trainee's perspective, some of these challenges may not be currently considered problematic.[20] However, similar to the protection of human research participants, protection of trainees is a fundamental responsibility of mentors, and this student-teacher relationship must be safeguarded.

For the scientific community, negative public perception and distrust of the biomedical research enterprise is perhaps one of the most worrisome challenges in academia-industry relationships. Recent public opinion research shows support for interactions between academia and industry.[21] On the other hand, lapses in judgment and reports of misconduct damage the public's faith in medical research.

CONFLICT OF INTEREST REGULATION

Rules and policies of the federal government, institutions, professional societies, and scientific journals guide the review and oversight of academia-industry relationships. Federal regulations (42 CFR Part 50, Subpart F) establish the standards for institutions to ensure there is no reasonable expectation that the design, conduct, or reporting of research funded under Public Health Service (PHS) grants or cooperative agreements will be biased by an investigator's conflicting financial interest. PHS guidelines provide *de minimus* standards for disclosure to the research institution while allowing institutions to implement review and oversight mechanisms in ways specific to their needs. The threshold for disclosure is $10,000 in annual income or equity in a relevant company or 5 percent ownership of such a company. Some institutions use a lower threshold for disclosure. Based on the PHS regulation, the National Institutes of Health (NIH) and the National Science Foundation require grantee institutions to maintain and enforce policies on conflict of interest and appropriately inform the agency of conflicts of interest. In addition, the Food and Drug Administration (FDA) regulations state that investigators who receive

compensation in excess of $25,000 from a corporate sponsor for a trial in which the investigator is engaged must disclose to the FDA at the time of filing for a new drug application.

Academic institutional policies are designed to protect the integrity of research, the missions of the institutions, stakeholders (including investigators, trainees and research participants), and public confidence.[22] Medical school conflict-of-interest policies vary widely, but policies governing research involving human participants are generally more stringent than for other types of research.[23]

Scientific journals, the major gatekeepers of research results, began adding disclosure requirements in their instructions to authors in the 1980s. The International Committee of Medical Journal Editors Uniform Requirements, adopted by 150 journals, includes guidelines for addressing conflicts of interest. A 1997 survey of 1396 highly ranked scientific and biomedical journals found that 16 percent had published conflict-of-interest policies.[24] Of those, 87 percent were medical journals. Nearly three-fourths of editors of those journals with policies publish author disclosure statements. A more recent survey (albeit with a smaller sample of forty-one biomedical journals) showed 59 percent of journals surveyed contained financial disclosure requirements in their published instructions to authors.[25] In addition, many scientific conferences require disclosures of financial interests in presentations.

ONGOING CHALLENGES FOR ACADEMIC INVESTIGATORS

Of course, one way to eliminate unintended negative consequences of academia-industry relationships is to eliminate the relationships themselves. But ending all academia-industry relationships is not a viable alternative. Such drastic measures are neither feasible nor beneficial to society. In fact, calls for *increased* collaborations between academia and industry are being heard.[26] By virtue of its increased participation in academia-industry relationships, the scientific community has indicated that the benefits outweigh the risks. The many medical advances academia-industry relationships have brought to society cannot be overstated. However, increased concerns about the integrity of medical research are evident. Although concerns about *potential* risks may not be well-aligned with *real* misbehavior, these issues must continue to be addressed by the scientific community to assure the credibility of medical research. The challenge for the scientific community is to disclose and manage these relationships.

The vast majority of biomedical researchers are guided by the highest ethical and professional standards. The focus of the report is to discuss and provide guidance to academic investigators to address challenges that may occur due to financial relationships between academia and industry, not to judge whether a real or perceived conflict of interest exists. Although the document is generally designed to address financial conflict of interest issues faced by individual academic scientists, some of the general principles apply to scientists broadly and address challenges that are not exclusively financial in nature.

Specific challenges for investigators discussed in this report include:

- ◊ How do investigators protect against research bias in industry relationships?
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- ◊ How do investigators address issues in entrepreneurial activities (start-up companies and technology licensing)?
- ◊ How do investigators with industry relationships minimize negative impacts on training and education?
- ◊ How do investigators with industry relationships protect against risks to human research participants?

CHALLENGES AND GUIDING PRINCIPLES

HOW DO INVESTIGATORS PROTECT AGAINST RESEARCH BIAS IN INDUSTRY RELATIONSHIPS?

Public support for research is built on a foundation of trust that reported research results are credible. Therefore, the potential for academia-industry relationships to bias research and investigators is a concern shared by the scientific community and the public. A challenge for investigators is how to address the perceived or real loss of objectivity when forging a relationship with industry.

Researchers diligently strive to maintain the objectivity and integrity of their investigations[3] by their:

- Intellectual honesty in proposing, performing, and reporting research;
- Accuracy in representing contributions to research proposals and reports;
- Fairness in peer review and collegiality of scientific interactions (including communications and sharing of resources);
- Transparency in industry relationships;
- Protection of human subjects and humane care of animals in research; and
- Adherence to mutual responsibilities between investigators and their research teams.[4]

Unfortunately, the perception of bias that results from having a financial interest can be damaging to the credibility of biomedical research. People understand money and its potential for influence. This potential for influence may cause public anxiety about financial interests in biomedical research. But the public may not understand the inherent checks and balances of scientific research designed to weed out research bias. Peer review and institutional review boards prevent investigators from obtaining or publishing any information that is not accurate or appropriately obtained. While recognizing the peer review system has limitations, ongoing review and revision is critical in minimizing individual subjectivity.

Guiding principle 1: Investigators have a responsibility and commitment to conduct scientific activities objectively and with the highest professional standards. These commitments and review processes must encompass all aspects of the research process (including research design, data collection, analyses, and communication of research results to the scientific community and the public) and professional responsibilities. This is a first and important step in addressing any challenges that may occur in financial relationships between academic investigators and industry.

HOW DO INVESTIGATORS WORK WITH INSTITUTIONS TO ENSURE REQUIREMENTS ARE FULFILLED AND RELATIONSHIPS ARE FAIRLY AND EFFECTIVELY REVIEWED AND OVERSEEN?

Federal law gives academic institutions the authority to develop and enforce policies governing relationships with industry. Concerns have been raised about the varying scope of

academic policies, why some policies are more stringent than others, and what the effects of this variation may have.[27, 28] The alternative is a uniform policy for all academic institutions mandated by the government or developed voluntarily by the institutional community. We do not intend to make recommendations on institutional policies. Rather, our focus is on describing the response of investigators to current institutional policies. This report considers whether or not it would make a difference in the lives of investigators if standard institutional policies, or some aspects of them, were implemented.

Most institutions use peer review to monitor industry relationships. These can take the form of institutional conflict of interest committees, for example. Challenges in using peer review committees include a "culture of collegiality," such that colleagues are not inclined to "police" their peers from their institution or outside their institution; a "culture of envy," such that peers are too strict when reviewing conflict-of-interest disclosures; and institutional conflict-of-interest issues. Investigators need to be aware of these dangers and guide their actions accordingly.

Guiding principle 2: The primary responsibility of full-time investigators is to the institutions. Outside activities shall complement, not compromise, institutional responsibilities. Technology transfer is one of the missions of academic institutions that serve the public interest. Investigators play an integral role in fulfilling this mission through their collaborations with industry. The challenge for institutions is promoting awareness and understanding of established requirements regarding such collaborations. To fulfill the perceived need of increased awareness of institutional requirements and potential challenges, a list of common institutional requirements appears in the Appendix. In addition, investigators must:

- ◊ Be aware of, and adhere to, their institutional policies on investigator conflict of interest and academia-industry relationships.

- ◊ Call for improvements within their institutions when the institutional conflict-of-interest policies are not clear or not sufficiently well disseminated.

- ◊ Consider specific aspects of institutional requirements *before* entering into and *throughout* their relationships with industry.

Guiding principle 3: It is appropriate and beneficial for academic institutions to develop and enforce their own mechanisms of review and oversight of investigator relationships with industry. In general, the non-uniformity of institutional policies of review and oversight does not appear to be a major challenge for many investigators; however, it is a problem for many institutional leaders**.** A major benefit of the discretion given to institutions by federal regulation allows institutions to be flexible to specific circumstances. Case-by-case review and oversight, guided by *rigorous* adherence to standards and rules, is the desired method of managing relationships. At the same time, some level of harmonization of institutional policies would be beneficial. In every case, private agreements must conform to institutional policies and guidance. More specifically, the academic research community should:

- ◊ Work towards common standards, while preserving case-by-case analysis and situational-driven decision making. Institutions should study the effectiveness of their policies and improve them based on input from investigators. This will help protect the investigator, the institution, the industry partner, and the public.

- ◊ Strive to develop uniform policies of disclosure of academic-industry relationships. Investigators would benefit from more uniform *disclosure* requirements.[29] The benefits of variable disclosure requirements are not clear and such non-uniformity may result in confusion and non-compliance by investigators. Although a specific model of institutional review and oversight is not endorsed, it would be beneficial to investigators if institutions used similar disclosure policies. These policies should be consistent in describing when disclosure occurs (annually, upon initiation of a relationship, or upon application for funding), and to whom (institutional committee, Dean, department Chair). Specifically, it is recommended that institutions ask all research investigators to *annually* disclose whether or not they have relationships with industry and to update this information upon starting or ending such relationships.

Guiding principle 4: The academic community can and shall monitor itself through *peer review* of industry relationships. Institutional committees that include peer members from the same institution are appropriate and effective in reviewing investigators' industry relationships. Peer review provides fair and effective review of industry relationships. Despite its challenges, peer review is the established, fundamental, and trusted adjudication mechanism of the scientific community. If the institution has rigorous standards and thorough training programs, this method of review and oversight should be effective and is in the interest of investigators and the public.

- ◊ If committees are not used for disclosure review, more than one individual should review relationship disclosures. This should occur regardless of whether the relationship was approved by the first person who reviewed it. For example, some institutions or departments review relationship disclosures "up the ladder" (first by a department chair then by a dean, or simultaneously).

- ◊ Committee composition, including the use of public representatives, is an important consideration. Several groups have endorsed having public members of the community in conflict-of-interest committees.[1, 2, 29] There are concerns, however, about confidentiality and proprietary information that may occur if committee members are not bound by confidentiality agreements. Institutions should carefully choose their public representatives and may have public representatives sign confidentiality agreements. Community members should be knowledgeable about ethical issues. They could include, for example, retired judges or lawyers not associated with the institution).

- ◊ Training for conflict of interest committees is crucial, especially the training of committee members not affiliated with the institution. Regular training and review of members should occur.

Guiding principle 5: Investigators want and need clear guidance, efficient processes, and adequate support mechanisms from their institutions during the disclosure and review process, and throughout their participation in industry relationships. Disclosure of relationships is the first step, but what is done once disclosure has taken place is critical part. Investigators need efficient, streamlined review of relationship disclosures. Investigators should be able to seek guidance from their institutions in this regard. The need for clarity is also true for policies from funding sources, professional associations, and journals. More specifically, institutions should:

- ◊ Act quickly in reviewing a new industry relationship for approval.

- ◊ Have a process for investigators to appeal decisions made by individuals or committees reviewing disclosures. The appeals process is an important safeguard for investigators.

- ◊ Consider using electronic databases for internal management of disclosure submission and review. Using electronic records would ease the burden on investigators, facilitate and expedite the administrative process, and provide better methods of communication and review between the necessary parties, including institutional review boards, technology transfer offices, and research offices. Electronic disclosure and review records should be "living" documents, not simply forms that are stored and not regularly updated. Extreme caution should be taken that personal and proprietary information is kept confidential.

- ◊ Make investigators aware of potential challenges that might be encountered during the relationship review process, and provide sources of information helpful in addressing these potential situations. Such institutional guidance and expertise would be particularly helpful to investigators if it was in the form of Frequently Asked Questions, case studies, or provides other tools and examples that highlight common challenges and provide guidance in resolving them.

- ◊ Clarify to investigators the consequences of non-compliance with their conflict-of-interest policies.

- ◊ Have statements that specify the basis for their approving or rejecting investigators relationships with industry.

HOW DO INVESTIGATORS ADDRESS ISSUES OF ACCESS, ANALYSIS, AND DISSEMINATION OF RESEARCH INFORMATION, DATA, AND MATERIALS IN INDUSTRY RELATIONSHIPS?

It is crucial that academic investigators be able to access, analyze, and disseminate research information, data and materials. Research success, promotion, and tenure depend heavily on information generation (through research that relies on access to data and materials) and dissemination (through publications, presentations, mentoring and teaching). Sometimes these academic principles conflict with industry's need to protect proprietary information and materials. When considering a relationship with industry, what principles and practices might help investigators address access, analysis, and dissemination of research information, data and materials?

Guiding principle 6: Investigators shall have access to, and be involved in the analysis and/or interpretation of all data generated in the research. All academic investigators participating in research (industry-funded or not) have a professional obligation to the integrity of the study.

- ◊ Logistical challenges in following this general principle may occur, especially in the case of multi-institution studies. A research committee or a principal investigator (PI) should be designated for the purpose of coordinating data access and analysis. This often works best when the PI and other key academics in a study with industry actually come to the company, work with the statisticians and others to access the database, ask questions, and challenge conclusions before finalizing the study results.

- ◊ Even in cases where a PI or research committee is used for data access and analyses, each participating investigator must be assured of the study's integrity in other ways. One way is to insist that research methods, including data selection and statistical analyses, are discussed and agreed upon by participating investigators *prior* to data collection.[30] This is standard operating procedure to help prevent bias from entering into data analyses.

Guiding principle 7: Mutual understanding of constraints, principles, and policies regarding access, analysis, and dissemination of research information, data, and materials among investigators and their students and trainees, institutions, and sponsors is beneficial. Mutual understanding of each parties' goals and constraints before and during the relationship will go far to ensure the success of the relationship.

- ◊ Once a study is published, academic investigators expect that effort will be made to provide data and materials to other investigators. This is often a condition of journal publication. Access to data and materials for use by other investigators in the field helps to validate research results, an important aspect of the peer review system. Every effort should be made to appropriately share data and materials for replication purposes.

- ◊ Some restrictions on access to information, data and materials in industry collaborations may have a legitimate rationale on the part of the sponsoring company. The industry sponsor does own the data and has regulatory responsibilities to FDA and others. For example, Guidelines for Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human subjects.[31] Compliance with this standard requires that the study sponsor take responsibility for data recording, reporting, quality assurance, analysis, and regulatory review for retaining these data. Companies must always adhere to these standards, especially when relationships with academia are to proceed in good-faith and be in the public interest.

- ◊ Academic investigators should always know and adhere to agreed upon design elements, including patient inclusion criteria for enrollment, in clinical studies. By not adhering to these criteria in a desire to enroll patients, the tested variable may be inappropriately used and the study flawed.

- ◊ Academic investigators should understand and be aware of specific contract terms, and enter into agreements only if they accept these terms. A list of useful questions is found in the Appendix. Investigators should honor the terms of industry agreements.

Guiding principle 8: Investigators shall not enter into agreements with companies that *prevent* publication of research results. Pre-publication review by an industry sponsor to secure intellectual property rights shall occur in a timely manner (no more than *thirty to sixty days*) so as not to unnecessarily delay study publication. This is in accordance with NIH guidelines for pre-publication review in sponsored agreements involving extramural grantees. There may be unique situations (e.g., multi-institution studies) when publication preparation and review may need more time. The terms of this additional time should be negotiated *before* the start of the study whenever possible. Investigators should accept some flexibility because not all problems can be anticipated before a study starts.

Guiding principle 9: Investigators shall be aware of and adhere to individual journal policies on disclosure of industry relationships. Journal policies vary with respect to author disclosure of industry relationships. Biomedical journals also vary widely in scope and audience and the types of research reported (clinical and basic research). Awareness on the part of authors and rigorous journal standards can be used as principles to protect against risk. Some consistency in journal policies would be beneficial because the variation in disclosure requirements may result in confusion and non-compliance by investigators.

- ◊ Journals with disclosure requirements should avoid requiring investigators to judge whether there may or may not be a relationship that could create bias and to simply require disclosure of relevant industry relationships.

- ◊ An author is generally considered to be someone who has made substantive intellectual contributions to a published study.[32] Investigators should be aware of their responsibilities regarding authorship and should not accept guest authorship of

"ghost written" manuscripts describing results of industry-funded studies. All authors must be prepared to accept accountability if the content of the article is questioned.[33]

HOW DO INVESTIGATORS OPERATE WITH TRANSPARENCY AND ACCOUNTABILITY IN INDUSTRY CONSULTING RELATIONSHIPS?

There are numerous benefits of consulting for investigators. These include:

- Financial gain (direct payments or access to grants);
- Iintellectual and personal growth through interaction with new colleagues;
- Insight into corporate life and product development;
- Access to information that can be used in one's own research;
- The honor and distinction in having been selected as a consultant; and
- The satisfaction of participating in the application of one's research.

Consulting relationships with the inventor of a licensed technology are often key to facilitating the development of the technology into a safe and marketable product. Industry employs academic consultants for their knowledge, insight, expertise, credibility, and prestige. They also benefit by having consultants facilitate drug development, disarm critics, and recruit employees.

But there are many challenges for investigators in their relationships with industry. There can be disputes of ownership of intellectual property generated in the consulting activity and the rights of future use of this property. It can be difficult to balance institutional duties with outside activities, especially if there are risks of legal liability, secrecy issues that could impinge on other duties, conflicts of interests in multiple consultancies, and rules that prevent participation in some research (such as clinical trials with a company while consulting). Private arrangements have the potential to interfere with what the institution and investigator can do in the future. These issues will only be exacerbated with the increase in interdisciplinary and multi-institution research. Investigators should be aware of these challenges before and during a consulting relationship and address any concerns with their institution. Investigators should pay careful attention to the consulting agreement they (or their institution) sign so as to insure compliance with the terms of the agreement.

Investigators look to their institutions for guidance in many issues related to academia-industry relationships. This is particularly true in consulting arrangements in which no standards are evident. It is the experience of some investigators that the lack of clear standards in consulting agreements is confusing and discourages some researchers from participating in these activities.

Guiding principle 10: Consulting and advisory board relationships shall be carried out in a transparent and accountable manner and be disclosed as they are initiated.
Investigators are primarily accountable to their institutions, but they also must uphold any industry contracts they have. It is important that these responsibilities are delineated.

- ◊ Transparency entails disclosure of relationships as required by institutions and journals, but also voluntary disclosure. Investigators should disclose all relevant industry relationships (including consulting) in publications and presentations.

- ◊ Investigators should keep their non-industry funded research and consulting activities as separate as possible and in accordance with each contract.[34] Companies choose experts in a particular field. Thus, keeping institutional duties and consulting activities separate is challenging for investigators. It is important that investigators demarcate institutional duties and any activities covered in a consulting contract.

Guiding Principle 11: When investigators have consulting relationships with investment firms related to their area of expertise, all parties shall be aware of the specific circumstances involved. Relationships between investigators and the investment industry are becoming more frequent. Almost one of ten U.S. physicians has such a relationship[35] and it is likely that some of these physicians are involved in research. Although many of the same benefits and risks exist for these relationships as with traditional consulting, there are unique characteristics worthy of attention. For example, there are many potential legal entanglements involving securities law and confidentiality agreements.[35]

- ◊ Investigators should be especially careful when a consulting relationship with the investment firm might overlap with relationships the investigator has with other companies (such as those potentially affected by the investment firm or those with which research is conducted).

- ◊ Investigators should not engage in premature communication of unpublished or non-publicly discussed information regarding ongoing research studies, particularly clinical trials, to individuals or organizations in the investment industry other than to a company sponsoring those studies.

HOW DO INVESTIGATORS ADDRESS ISSUES IN ENTREPRENEURIAL ACTIVITIES?

Academic institutions are more frequently licensing inventions to companies. The growth of licensing activities has given rise to questions about whether and under what circumstances institutions should license technology to a company in which investigators or other members of the institution have financial interest. There are many benefits in investigator participation in entrepreneurial activities (start-up companies and technology licensing). Challenges for investigators include the potential to bias research to encourage company growth, the potential harm to individual and institutional reputations, and conflict of commitment with other institutional responsibilities. Often, a condition of consulting contracts is that discoveries are owned by the sponsor if relevant to the consulting area. Conflicts between industry sponsors and institutions can occur when intellectual property issues arise. For the individual scientist, the challenge is how to participate in these activities in a transparent and accountable manner and address any challenges that may arise with their institutions (ideally, before they develop into serious disagreements).

Guiding principle 12: Investigators shall not use federal funds to the benefit of a company, unless this is the explicit purpose of the mechanism used to fund the research. These mechanisms include projects funded by Small Business Innovation Research or Small Business Technology Transfer grants. The goal of technology transfer is to translate basic research findings into useful products, and start-up companies based on an institutional license are often an important mechanism for accomplishing this goal. The inventor of a technology often has the most expertise that helps to translate that technology into a useful product. Investigators with dual roles (research faculty and company founder/consultant) face challenges of potential overlap of research interests, thereby blurring the line between institutional responsibilities and outside interests.

Guiding principle 13: When investigators own significant equity in a company with which research is conducted, all parties shall be aware of the special circumstances involved. Equity is an important mechanism of compensation, particularly for small start-up companies, and can be an effective incentive for academic investigators. There are several types of situations in which equity is used as compensation. For example, an investigator may have both a research relationship and a managerial role in a start-up company based on an institutional license. In this case, the institution is involved as owner of the licensed technology, and the terms of the relationship can be negotiated between the institution and investigator**.** It is important that investigators understand that equity poses unique challenges and risks because it has a larger *potential* for financial gain than other forms of compensation, such as consulting fees or research grants. As a result, the potential for conflicts of interest is substantial. Equity relationships need diligent monitoring because the value of the compensation varies according to the perceived success of the company. Investigators holding supervisory roles in the university should pay special attention to risks.

Guiding principle 14: When holding a significant role in a start-up company, investigators shall be guided by agreed-upon limits to the scope of the relationship. Significant roles include serving as a member of a board of directors, chief scientist, or any executive level position. Close interaction between the inventor of the technology and the licensing company is often beneficial. As company founders, investigators may need to participate broadly in the company's development. Investigators should always submit the proposed activity to the institution and follow institutional requirements.

- ◊ It is appropriate (and often necessary) for an investigator to serve *initially* in a managerial role. Activities may include consulting, review of strategic plans, and discussing the company's progress. A contract should be used to define activities and method of compensation. The investigator should be replaced as soon as possible to avoid misappropriation of resources, perception of inappropriate actions, or inappropriate remuneration.

- ◊ The company should not be provided knowledge of or access to institutionally-generated/federally funded research prior to the time they are made available to the scientific community at large.

Guiding principle 15: Investigators shall be aware of and adhere to requirements of federal funding related to disclosure of inventions. Investigators shall adhere to patent law and institutional requirements. An obligation of the Bayh-Dole Act is that federal grantees must disclose inventions resulting from federally-funded research to their institutions. Investigators may lack awareness of this requirement**.** Proper disclosure policies and procedures should be followed, and investigators should not condone moving technologies and discoveries "out the back door" to companies with which they have a relationship.

Guiding principle 16: Investigators shall not seek to influence their institution's technology transfer decisions for personal gain. It is recognized that investigators often have a financial interest in companies and that the resulting potential for conflicts of interest requires oversight and resolution. In some cases, the expectations of the investigator may not be in line with the interests of the institution. Institutions own intellectual property resulting from an investigator's federally-funded research. Whether or not the individual is involved in licensing arrangements is up to the institution. Government guidelines might be helpful, but investigators should always go to their institution first.

- ◊ Investigators should understand their institution's royalty distribution policies and standards for licensing. Investigators expect that the institution will provide ways for inventors to participate in, and benefit from, the commercialization of their discoveries. Institutions should consider practices that will continue to provide incentives to investigators.

- ◊ Situations may occur when royalty income causes difficulties between investigators (e.g., an investigator that provided assistance may find fault in not being listed as an inventor of the patent and thus entitled to royalty shares). Patent law requires including collaborating inventors (including trainees), and there are defined criteria for who is an inventor and who is not. These criteria are different from who might be included as an author on a paper, and investigators should be cognizant of this distinction. Investigators and trainees have an obligation to understand their institution's policies and should seek institutional guidance if they have questions.

- ◊ Investigators may face challenges regarding restrictions on future rights of use from industry sponsors. Institutions should retain the rights to use the patented invention for research purposes, and have the ability to transfer that research right to other not-for-profit research institutions.

HOW DO INVESTIGATORS WITH INDUSTRY RELATIONSHIPS PROTECT AGAINST NEGATIVE IMPACTS ON TRAINING AND EDUCATION?

For the purposes of this report, a "trainee" includes students, postdoctoral fellows, residents, and investigators or faculty members that are not PIs. Investigators should also consider potential impacts on subordinate employees. Mentoring and educating trainees is an important (and sometimes primary) responsibility assumed by academic investigators. The relationship between a mentor and trainee is a close one that is based on trust. Often inherent

in this relationship is an unequal distribution of power and influence between the individuals in the relationship. As a result, the person being mentored may not feel he/she has the freedom to refuse the mentor's request. In addition, whenever the possibility exists that a mentor's advice or counsel might be influenced by personal financial interests, then there also exists the potential for significant negative impacts to the training or career development of the person being mentored. Potential financial conflicts of interest may occur in any relationship when there is a real or perceived imbalance in power or influence between a mentor, advisor, or supervisor and a student, trainee, or junior colleague, and the potential exists for significant financial benefit to the more powerful individual.[36]

Guiding principle 17: A mentor's outside commercial interests shall avoid impeding a trainee's timely progress toward his/her degree, restricting a trainee's right to publish his/her research in a timely manner, compromising a trainee's career progress, or restricting a trainee's freedom of inquiry.

- ◊ The institution, mentor, and trainee should discuss and agree upon a definition of "timely" prior to the start of trainee involvement.

- ◊ Any agreements that would place restrictions on trainee activities must be fully disclosed to the institution, department and trainee and the implications described *prior* to their involvement in the research.

- ◊ Sources of information and institutional contacts should be provided to trainees that will help them understand these issues, answer any questions, and make fully-informed decisions.

- ◊ If the nature of the research with an outside sponsoring organization requires pre-publication review beyond sixty days, investigators should seriously wonder whether trainees should be involved in the studies. Substantial delays in publication have adverse effects on a trainee's progress.

Guiding principle 18: Mentors and institutions should make trainees aware of their rights and responsibilities in industry relationships. Trainees may have a direct relationship with a company, such as a training or travel grant, or an indirect relationship through their mentor. It is important to understand whether such relationships involve restrictions or are unrestricted benefits from industry to foster education, which improves the future work force.

- ◊ Institutions should consider whether or not students should be involved in the disclosure process at institutions, as well as other opportunities for training on academia-industry relationships and conflict of interest.

- ◊ Trainees have rights under patent law to be designated as an inventor of a technology, if appropriate.

HOW DO INVESTIGATORS WITH INDUSTRY RELATIONSHIPS PROTECT AGAINST RISKS TO HUMAN RESEARCH PARTICIPANTS?

Conflict of interest is not exclusively a clinical research challenge. However, the potential for risks to human research participants is a higher level of risk than with basic research. Investigators and institutions have a responsibility to maximize the benefits to research participants, while ensuring their protection against any negative consequences of competing interests. More stringent institutional review is appropriate, and many medical schools conducting research apply such stringency.[23] The Association of American Medical Colleges issued recommended guidelines for the oversight of individual financial interests in research involving human participants in 2001.[2] One of the core principles is that *institutions* should regard all significant financial interests in human subjects research as potentially problematic and, therefore, requiring close scrutiny. Central to the recommendations is a rebuttable presumption that in the presence of significant financial interests (defined as more than $10,000 or 5% equity ownership in any one relevant company), the research should not be conducted by the affected individual or in that institution, absent compelling circumstances. In a 2004 survey of member medical schools, sixty-one percent had adopted the rebuttable presumption or similar standard, [23] indicating a positive reaction to this recommendation.

There are many types of research involving human participants from basic research to clinical trials. Even within the realm of clinical trials, different benefits, risks, and protections occur. For example, medical device and surgery research can have different profiles of risks and rewards than pharmaceutical research. Phase III trials may pose greater potential for financial gain; however, there are more protections against bias due to the fact that they are larger, conducted at multiple centers, and are double or triple blinded. Phase I trials may be more susceptible to the influence of single investigators, but may be impossible without a committed investigator who also comes with financial interests (for example, the inventor of the technology being tested). Even when it is possible to exclude an investigator with financial interests, it may not be in the best interest of the public if that conflicted investigator has the most knowledge and expertise to carry out the study. For example, the researcher may be a surgeon who has developed a unique surgical technique. All of these issues should be considered.

Guiding principle 19: *Investigators* shall regard all significant financial interests in research involving human subjects as potentially problematic and thus as requiring close scrutiny.

- ◊ Case-by-case review and oversight, guided by rigorous standards should be used. The balance of benefits and risks to patients and the research should be considered by both institution and investigator in every case. Phases of clinical trials have different benefits and risks, and each case should be judged on those circumstances. In addition, investigators should understand that some institutional review boards may require that information regarding relevant financial relationships be disclosed to patients and human research participants so that they may make fully-informed decisions about their participation.[37]

◊ Investigators with significant financial interests should not play a role in the research, absent compelling circumstances.[2] If they are involved, they should not solely determine experimental design or data analyses. These aspects of the study should be decided upon by peer-review mechanisms using investigators without financial interests in the study outcome.

CONCLUSION

Academia-industry relationships ultimately have the ability to bring multiple resources to scientific advancement and the battle against disease. It is only through such relationships that advancements in the life sciences can most rapidly achieve the maximum benefit to society. Clinical and basic science investigators benefit from industry relationships through increased resources to support on-going projects, interactions with colleagues that facilitate the bidirectional flow of knowledge and materials, and participation in the application of research.

Investigators are individually responsible for maintaining accountability in their choices to enter into relationships with industry, complying with institutional, government and journal policies, and taking responsibility to guard against bias in research. The scientific process requires scientists to work within a culture of the highest standards for research and professional conduct, and to identify and manage conflicts of interest as an inherent responsibility of their job. They must continue to make efforts to provide access to research results and disseminate findings in a timely manner. Finally, they must protect against risks to human research participants and trainees.

In light of the increased frequency of academia-industry relationships, the scientific community must continue to examine and manage these relationships to maximize the benefits and guard against the risks. Both industry and academic institutions should work together to steer investigators away from key challenges and roadblocks, including challenges arising from financial relationships. The broader scientific community (including academic institutions, journals, and scientific societies that represent investigators) has a shared responsibility to provide clear and rigorous standards, fair and efficient review and oversight of relationships, and adequate guidance to investigators before and throughout relationships with industry.

Investigators who satisfy all institutional requirements for disclosure and oversight, are aware of the challenges, and have made smart decisions based on guiding principles to address these challenges will minimize negative consequences of academia-industry relationships. In some cases, prohibitions of specific activities may be necessary. Also, individuals may decide not to enter into a relationship based on their own analyses of benefits and risks. This type of individual assessment is encouraged.

The purposes of the guiding principles presented in this report are to help academic investigators become aware of potential challenges in academia-industry relationships, encourage awareness of requirements and interaction with their institution in addressing these challenges, and promote voluntary measures for operating with transparency and accountability. While the document was generally designed to address financial conflict-of-interest issues faced by individual academic scientists, some of the general principles apply to scientists broadly and address challenges that are not exclusively financial in nature. The vast majority of biomedical researchers are guided by the highest ethical and professional standards. Scientists must continue to uphold practices that advance the public good,

including identifying and addressing conflicts of interest. There are legitimate benefits to *all types* of academia-industry relationships. With careful disclosure and oversight, the risks can be minimized or eliminated and the benefits to the scientific community and public maximized.

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APPENDIX

Academia-industry relationships: Arrangements in which academic scientists, administrators, and institutions carry out research or provide intellectual property to industry in return for considerations of various types such as research support, honoraria, consulting fees, royalties, and equity.

Are you considering, or do you currently have any of the above relationships? If so,

1. What are your institution's requirements for disclosure of industry relationships?

    a) What criteria are used for defining a conflict of interest? What are the thresholds for disclosure?
    b) Must you disclose to the department Chair, Dean or other supervisor; institutional committee or university official; legal counsel?
    c) When must you disclose (annually, ad hoc basis, upon application for funding, prior to signing an agreement)?
    d) Must you disclose this in publications, presentations or to research participants?
    e) What types of relationships must you disclose (funding, consulting arrangements, company boards, equity, etc.)?
    f) What are the penalties for non-disclosure?

2. What are your institution's policies on investigators having financial interests (equity, royalties, consulting fees, membership on a board of directors, etc.) in a company sponsoring your research?

3. What are your institution's policies on investigators having financial interests in a company sponsoring clinical research involving human participants?

4. What are your institution's policies on the use of institutional resources and personnel in outside activities (e.g. consulting)?

5. What are your institution's policies involving trainees in industry-funded research?

Are you considering entering into any of the above relationships with a company? If so, please consider the following *prior* to the start of the relationship:

1. What are the conditions of publication?
2. What are the conditions of ownership and access of research data and materials? What are these conditions in multi-institution research projects? Do any of these conditions conflict with any institution's policies?
3. How are experimental designs negotiated?
4. What types of compensation are paid, and for what work?
5. What are patient inclusion criteria for enrollment?