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Analysis & Perspective

Conflict of Interest

Conflicts of Interest in Human Subject Research: Adapting to Evolving Best Practice Standards

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INTRODUCTION

With the adoption of the Bayh-Dole Act in 1980 emerged a new federal policy endorsing and encouraging institutions to seek private investment for research and allowing institutions and individual researchers to share in the financial return generated from inventions produced through research initiatives. Beginning in 2000, however, several high profile cases involving harm suffered by human subjects participating in clinical trials cast a broad and bright light on whether such financial interests give rise to potential conflicts of interest that generate bias on the part of institutions and researchers and, in turn, pose significant risk to the safety of clinical trial subjects¹

That potential risk to human subjects has since become the focus of intense and widespread scrutiny by Congress, regulatory agencies, trade associations, patient advocacy groups, and the national media. Their call for conflicts-of-interest reform in human subject research is loud and clear, and it pertains to all types of human subject research, whether industry-sponsored, government-funded, or investigator-initiated, and to both individual and direct, indirect, and imputed institutional conflicts of interest. At the heart of their message is a demand for greater transparency, a practical but effective approach to management or elimination of conflicts, and increased governance oversight of and accountability for conflicts of interest in research compliance. Institutions and investigators who fail to heed this call undoubtedly will assume increased risk of liability for personal injury; periodic, high-profile and potentially intrusive and disruptive government investigations; suspension or termination of research activities; loss of federal funding; false claims liability; and long-term or fatal damage to the reputations of researchers and research programs.

What is clear now for all organizations and programs, whatever their size, complexity, and sophistication, is that (1) the federal conflicts-in-research baseline is unlikely to be enough, and (2) what is adopted should be capable of meaningful implementation and enforcement. Just over 25 years since the policy shift established by the Bayh-Dole Act, the current challenge is to establish and maintain a conflicts-of-interest infrastructure that achieves the right balance between promoting and supporting a spirit of innovation on the one hand and adapting to the best practice standards that are emerging from the widespread cry for reform on the other.² This article reviews current federal legal and regulatory requirements and emerging best practice standards for identifying, assessing, and managing conflicts of interest in human subjects research,³ and discusses the

nature and extent of the conflicts addressed by such requirements and standards⁴ It also provides insights prioritizing and adapting to emerging best practice standards in the effort to achieve that balance.

CURRENT LEGAL STANDARDS

Current federal laws and regulations governing conflicts of interest in research vary in their focus and approach in several key respects: who is obligated to make the disclosure of potential conflicts, when and to whom disclosure must be made, the scope and purpose of the required disclosure, whether they address management of conflicts, and the degree to which they prescribe the overall content and approach to conflicts policies and procedures. The Public Health Service's ("PHS")⁵ conflict requirements, for example, apply only to federally funded research (unless the applicable institution has agreed to abide by federal guidelines for all private research as well in research conducted under their federal-wide assurance),⁶ require disclosure of conflicts to the institution before grant applications are submitted to a PHS agency, and provide considerable detail concerning the disclosure, assessment, and management process.⁷ The Food and Drug Administration's ("FDA") regulations, on the other hand, apply to research designed to obtain market approval for FDA-regulated products (regardless of funding source), focus on the integrity and objectivity of the study data and results, and require that disclosure be made before FDA market approval is granted rather than before the research begins.⁸ Both the PHS and FDA requirements address only disclosure of individual interests of study investigators (not institutional interests), and use financial disclosure thresholds and methodologies that require disclosure of only "significant" interests held by the investigators. The 2004 Department of Health and Human Services ("DHHS") guidance on financial relationships and interests in human subject research⁹ is by its nature non-binding and more general than the PHS and FDA requirements, but represents the first official, federal pronouncement addressing institutional financial conflicts of interest in research.

While these federal conflicts-of-interest laws fall short of emerging best practices, it is nonetheless important to understand them as a baseline and framework for developing research program conflicts-of-interest policies and procedures.

The PHS Conflict-of-Interest Framework

All research funded by a PHS grant or cooperative agreement except for Small Business Innovation Research ("SBIR") Program Phase I applications must comply with the PHS regulations governing objectivity in research that were implemented to ensure that the design, conduct, or reporting of such research will not be biased by conflicting financial interests of an investigator, or the investigator's spouse or dependent child (collectively defined as "Investigator").¹⁰ To apply for a PHS grant, an institution must have in place written and enforced policies to identify and manage, reduce, or eliminate conflicting financial interests.¹¹ The regulations also require that an institution have in place a mechanism to enforce and, where appropriate, sanction noncompliant disclosure activities.

Internal Disclosure. At the time an institution applies for a PHS grant award, the institution must require any Investigator who may conduct PHS-funded research to disclose to the institution any "Significant Financial Interest" ("SFI") that (1) "would reasonably appear to be affected by the research for which PHS funding is sought," and (2) is in an entity whose financial interest would reasonably appear to be affected by the research.¹² An SFI includes "anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interests (e.g., stocks, stock options or other ownership interests); and intellectual property rights (e.g., patents, copyrights and royalties from such rights)"¹³ except: (a) salary, royalty, or other payments from the institution applying for the PHS grant, regardless of amount; (b) any ownership interest in the institution if the institution is an applicant under the Small Business Innovation Research Program; (c) income from seminars, lectures, or advisory committees for public or nonprofit entities; (d) income from services on advisory committees or review panels for public or nonprofit entities; (e) equity interests of less than \$10,000 that do not constitute greater than 5 percent ownership interest in any single entity; or (f) salary, royalties, or other payments that are not expected to exceed \$10,000 over the next 12 months.¹⁴ These disclosure thresholds apply in the aggregate to the Investigator (including his or her immediate family).¹⁵ SFIs disclosed by each Investigator must be updated annually or more often if new reportable interests are obtained by Investigators during research.¹⁶

Assessment and Management of Disclosed Interests. Once an Investigator has disclosed SFIs to the institution, a designated institutional official must determine whether these interests constitute a "conflict of interest," and if so, what actions should be taken to manage, reduce, or eliminate such conflicts. A "conflict of interest" is deemed to exist "when the designated official reasonably determines that a [SFI] could directly and significantly affect the design, conduct or reporting of the PHS funded research."¹⁷ The PHS regulations do not prescribe the method for managing, reducing, or eliminating conflicting financial interests, but they offer the following suggestions: (1) public disclosure of the SFI; (2) monitoring of research by independent reviewers such as data safety monitoring boards; (3) modification of research plan (e.g., require that the negotiation of relevant research affiliations or other contracts be handled by a disinterested person within the institution); (4) disqualifying the disclosing Investigator from participation in all or some portion of the PHS-funded research; (5) divestiture of the SFI; or (6) severance of relationships that create actual or potential conflicts, (e.g., resignation from management positions or government boards that create actual or potential conflicts).¹⁸ The Association of American Medical Colleges, a well-respected leader in the arena of conflicts-of-interest management, also has suggested that using study design approaches that help to prevent the introduction of bias into research projects (e.g., double-blinded or randomization techniques) and establishing a means to verify research results (e.g., independent collaboration with other labs and/or FDA review) also may reduce potential bias resulting from conflicting interests.¹⁹

Disclosure or Reporting Obligations. Prior to any expenditure of PHS grant funds, the institution must report to the PHS Awarding Component (i.e., the organizational unit of the PHS that funds the research) the existence of a conflicting interest identified by the institutional official, and provide assurances that this interest has been managed, reduced, or eliminated.²⁰ An institution is *not* required to disclose the nature of the interest or any other details. Rather, it must simply report the existence of a conflicting interest, and the management of that interest. If a conflicting interest is identified after the institution's filing of the initial report under the award, the institution must file an interim report of conflicting interest within 60 days of identification of the interest.²¹ Institutions are also obligated to "promptly" notify the applicable PHS agency of an Investigator's noncompliance with the institution's conflicts-of-interest policy if the noncompliance biased the design, conduct, or reporting of the PHS-funded research.²²

The institution's notification to PHS also should include a statement of the corrective action taken or proposed to be taken to remedy the situation. Examples of possible corrective actions include: withdrawal or correction of all pending or published abstracts and papers emanating from the research; removal of the responsible person from the particular project; letter of reprimand to the investigators; special monitoring of future work; probation; suspension; salary reduction; or initiation of steps leading to possible rank reduction or termination of employment.

The instructions to the NIH grant application²³ and the NIH Grants Policy Statement,²⁴ provide that the authorized institutional official signing the application is deemed to certify that: 1) the institution has a written and enforced administrative process to identify and manage, reduce, or eliminate conflicting financial interests with regard to NIH-funded research projects; (2) prior to the expenditure of NIH funds, the institution will inform NIH of the existence of any conflicting financial interests in the PHS financial interest regulations and will assure NIH that the interest has been managed, reduced, or eliminated in accordance with the regulations; (3) the institution will continue to make similar reports on subsequently identified conflicts; and (4) the institution will make information available to NIH, upon request, regarding how identified conflicting interests have been mitigated.²⁵

FDA disclosure requirements apply to study sponsors such as pharmaceutical and device manufacturers (as opposed to the researcher or host institution) and focus on whether relationships exist that may jeopardize the reliability of the data submitted to the FDA.²⁶ The FDA regulations apply to any entity sponsoring a "covered clinical study" that is the basis for an Investigational New Drug ("IND") or Investigational Device Exemption ("IDE") application supported by clinical data.

The FDA Form 3455 requires disclosure of "significant payments of other sorts" from the sponsor, which means payments from the sponsor of more than \$25,000 not related to the conduct of that particular research study.²⁷ The form also requires disclosure of any "significant equity interests" held by the investigator in the sponsor. "Significant equity interests" means any interest in a privately held entity or more than \$50,000 in a publicly traded company.²⁸ The FDA reserves the right to impose audit requirements on the study, require further analysis to evaluate the reliability of the data, and even refuse to regard the data produced by a

conflicted investigator as reliable for purposes of FDA approval.²⁹

Notably the disclosure of the financial relationship comes after the study is completed and the marketing application is filed with the FDA. This does not mean, however, that sponsors should not inquire about financial arrangements at the beginning of a study and monitor such arrangements during the study. Both the IND and IDE regulations³⁰ provide that, before allowing a Clinical Investigator to begin participation in an investigation, the IND/IDE sponsor must obtain sufficient accurate financial information that will allow an applicant to submit the required certification or disclosure statement required under the regulations.³¹ Therefore, the sponsor should obtain this information prior to the start of the study to ensure that any financial relationship is identified and the impact minimized, so when the data are due to be submitted with the marketing application, no question exists as to their reliability.

DHHS Guidelines

In May 2004, DHHS published a document titled, *Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection* ("Final Guidance").³² Developed in response to a series of government reports and public conferences identifying and addressing the need for various reforms in the government's oversight of human subject research,³³ this guidance document specifically focuses on the need to address both institutional and individual conflicts of interest and raises the possibility of forming a committee separate from the IRB to address conflicts of interest in research. As discussed further below, both of these features of the guidance have found their way into emerging best practices standards.

The focus of this document is on general protections rather than specific proscriptions that should be established in an effort to comply with the PHS conflict-of-interest regulations.³⁴ Its key components are: (1) final guidelines for the research community to utilize in assessing whether financial interests in research may adversely affect the rights and welfare of human subjects; (2) a uniform statement of policy addressing all research that is either supported by DHHS or regulated by the FDA; and (3) recommended actions that may be taken by institutions, their conflict-of-interest committees, investigators, and institutional review boards ("IRBs") to manage these conflicts, including institutional conflicts, and to protect human subjects. DHHS recommended that institutions establish a separate conflict-of-interest committee that is charged with addressing individual and institutional conflicts of interest in research, is distinct from the IRB (but communicates with the IRB), develops procedures for capturing institutional conflicts of interest and for providing training on conflicts of interest generally, and is independent from the management of institutional finances. It further recommends that the institution consider using "independent organizations to hold or administer the institution's financial interest." For Investigators, DHHS recommends inclusion of information about a financial arrangement and the management of such arrangement in the written informed consent and possible use of a disinterested party to obtain consent and/or of an independent body (e.g., data and safety monitoring committee) to monitor the research.

False Claims Liability Based on Conflicts of Interest in Research

For purposes of federal grants, researchers must certify in their grant application that they are in compliance with certain statutory and regulatory requirements. In most cases, making such a certification is a prerequisite to being awarded a grant. The False Claims Act ("FCA")³⁵ prohibits a person from inducing the government to pay money when the person has knowingly given the government false information. Researchers who provide false certifications of compliance because of failure to disclose conflicts of interest thus could be subject to liability under the FCA, in addition to the common law claims discussed above.³⁶

Related Federal Research Compliance Consideration: Research Integrity and Misconduct

The PHS regulations on Research Misconduct³⁷ include a set of federal research compliance policies applicable to federally funded studies (including support provided through contracts and direct funding of PHS intramural research in addition to grant funding and cooperative agreements). The Research Misconduct regulations are designed to protect the reliability of research data and the independence and integrity of the clinical trial enterprise.³⁸ They define research misconduct as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research or in reporting research results.³⁹

Instances of research misconduct can be motivated, at least in part, by the types of financial and associational interests that give rise to potential conflicts of interest, and thus the lines between the two often are blurred in the eyes of the media and the public. While a strong conflicts-of-interest policy likely will prevent significant bias from affecting, or appearing to affect, the integrity of research results, it is not enough. The research misconduct regulations specifically require the development of policies and procedures for reporting and responding to allegations of research misconduct. Accordingly, no research compliance program will be complete without well-developed and well-integrated policies, procedures, and forms that address both conflicts of interest and research integrity and misconduct and that are strictly and uniformly implemented and enforced.

EMERGING BEST PRACTICE STANDARDS

The following recent developments have raised the bar for conflicts of interest in research above the baseline established by the federal regulatory scheme. They are indeed both the catalyst for and the source of evolving best practices in conflict of interest in research compliance.

Case Law

Litigation involving harm to human subjects in clinical trials has used failure to disclose conflicts of interests as a basis for various types of claims, including misrepresentation and fraud. As recently noted by one federal prosecutor,⁴⁰ cases alleging that researchers had conflicted loyalties are likely to have jury appeal.

In a widely known California case, the court held that doctors who did not disclose a financial conflict of interest to a patient failed to secure informed consent.⁴¹ In a lawsuit filed against the University of Pennsylvania, the parents of Jesse Gelsinger, an 18-year-old subject who died in a gene therapy clinical study, alleged that the university failed to disclose that the principal investigator in the study had roughly \$14 million worth of equity in the industry entity sponsoring the trial.⁴² In March 2001, a class of plaintiffs representing 80 subjects who died in a clinical trial at the Fred Hutchinson Cancer Center filed a lawsuit claiming that failure to disclose to the subjects the \$3 million in stock and payments that the investigators received from the sponsor of the research in 1983 (later valued at \$14.5 million) and to manage or eliminate the conflict arising from such interest, supported claims for breach of the subjects' rights to be treated with dignity, common law fraud, intentional misrepresentation, assault and battery, and product liability.⁴³ In a complaint filed in the Pennsylvania courts in 2002, the widow of a deceased subject of a clinical trial asserted that the subject should have been informed that the physician the sponsor appointed to be the subject's advocate was employed and paid by the sponsor.⁴⁴ In July 2003, a participant in a clinical trial sued the industry sponsors, the IRB, the physician, and the clinical research organization ("CRO") managing the trial alleging, in part, common law fraud, intentional misrepresentation, and constructive fraud based on failure adequately to disclose a conflict of interest.⁴⁵

Media Coverage

The media coverage of conflicts of interest in research has become almost relentless, particularly at the national level. Without drawing clear lines (and often blurring the lines) between research conflicts and clinical conflicts, individual and institutional conflicts, and conflicts of interest and research misconduct, the resounding theme of both the national and local press coverage is the need for higher standards of ethics and integrity in research. At times, the media have been the drivers, rather than just passengers, of the conflicts reform bandwagon.⁴⁶ The intensity and frequency of media attention mandates the development of compliance approaches that meet a higher standard than strictly required by law. An important component of such new approaches will be identifying and managing the risk arising not only from the presence of an actual conflict but also from even the mere appearance of a potential conflict.

Trade Association Reports Calling for Improved Conflicts Standards and Practices

Undoubtedly in response to the calls for research reform focused on patient safety, the various trade associations representing academic medical centers, universities, physicians, and pharmaceutical and device

manufacturers have undertaken studies and produced guidance documents concerning individual and institutional conflicts of interest in research. The recommendations articulated in these guidance documents have significantly advanced the conflicts reform movement, and they are rapidly evolving into best practice standards that are either being implemented or seriously considered by the various participants in biomedical research activities.⁴⁷ Notable among these recommendations and best practices are the following: (1) increasing disclosure to human research subjects; (2) recognizing the distinction between individual and institutional conflicts of interest; (3) establishing a committee or other body other than the IRB to be responsible for important aspects of the conflicts disclosure, assessment, and management process; (4) establishing appropriate communication between the conflicts review body of the institution and the IRB; (5) including individuals with appropriate independence and expertise on that body (*e.g.*, a community member); (6) strengthening standards for independence of IRB members; (7) separating an institution's research administration from administration responsible for its overall investment and research commercialization initiatives; (8) applying the same conflicts-of-interest standards to all research, regardless of funding source; (9) more rigorous policies and procedures for identifying and managing research conflicts of interest premised on a rebuttable presumption against significant financial interests held in connection with human subject research; (10) lowering or abandoning current disclosure thresholds; (11) improved education for research program participants, including members of IRBs and conflict committees; (12) more formal and thoughtful approaches to development of conflict management plans, as well as monitoring and oversight of compliance with those plans; and (13) transparency in reporting of research results (particularly adverse events and identified risks).

CORRESPONDING CONFLICTS COMPLIANCE PLANNING CONSIDERATIONS: BALANCING BASELINE LEGAL STANDARDS AND EMERGING BEST PRACTICES

An organization must take these emerging best practices into account in the development, assessment, and modification of any conflicts of interest in research compliance policies and procedures. As with any component of an overall corporate compliance program, however, the extent to which best practices can and should be adopted and effectively implemented will depend on various factors, including the degree of the risks presented and the size and complexity of the organization and its research program. For large academic medical centers, adopting more rather than less in the near term may be an imperative. For a community or regional health system whose research program is early in its growth and development, a case can be made for a "scalable approach"--being selective in the practices implemented in the near term, while phasing in comprehensive reform over time. What is clear for all organizations that serve as research sites for human subject research, whatever their size, complexity, and sophistication, is that (1) the federal conflicts in research baseline is unlikely to be enough, (2) the organization must assume principal responsibility for conflict-of-interest compliance and adopt research conflict policies and procedures for fulfilling that responsibility so that the IRB is not the sole body handling conflicts, and (3) what is adopted must be capable of meaningful implementation and enforcement.

The following discussion provides insights for prioritizing and adapting to emerging best practice standards.

CONFLICTS POLICY

Definition of Conflict of Interest

A cornerstone of any research conflicts compliance infrastructure is the definition of conflict. Several changes to definitions commonly used in the past should be considered minimum requirements in any conflict policies and procedures going forward.

Appearance of Conflict. The PHS requirements provide that a "conflict of interest" is deemed to exist "when the designated official reasonably determines that a [SFI] could directly and significantly affect the design, conduct or reporting of the PHS funded research."⁴⁸ In contrast, both AAMC and AAU have adopted the following definition: "The term individual conflict of interest in science refers to situations in which financial considerations may compromise, or *have the appearance of compromising*, an investigator's professional judgment in conducting or reporting research. Addressing appearance of conflict in both the definition and the corresponding procedures for disclosure, assessment, and management of conflicts, and having the conviction to forego

opportunities that create the mere appearance of a conflict, will be essential

Associational Interests Both the current federal scheme and some of the emerging best practice guidance documents emphasize disclosure and management of financial interests that can create conflicts risk. A focus only on financial interests now clearly is too narrow. Associational interests also have potential for generating bias in research, which in turn can result in patient harm, and threats to the integrity of research data and analysis. An associational interest occurs when an individual (e.g., investigator or other member of the research team) has a formal or informal, non-financial relationship or involvement with a sponsor of research, or with an entity that has a direct or indirect financial interest in the sponsor or otherwise stands to benefit from the results of the research study. Examples include an uncompensated position on an industry sponsor's scientific advisory board, board of directors, or authorized committee of the board of directors, service on a board of a venture capital fund that invests in the sponsor, and co-investment with the sponsor in a venture capital fund or start-up entity.⁴⁹

Individual Conflicts of Interest. Even the AAMC and AAU expanded definition of individual conflicts of interest may be too narrow because it focuses on the potential for conflicts arising from interests held by an investigator. Potential conflicts arising from the interests of any member of the research team, not just the investigators, and of family members of the team, should be identified, assessed, and managed. How "family member" is defined varies as to whether it should include only members of the immediate family and if so, which ones.⁵⁰ In any case, having the policy governing conflicts of interest in research apply to all members of the research team and appropriate members of their families should be considered a minimum requirement in conflicts compliance reform efforts.

Institutional and Imputed Conflicts of Interest. The DHHS final guidance is the only federal regulatory authority that addresses institutional conflicts of interest, and it provides only guidance, not mandates. The clear message emerging from the media and industry association reports is that addressing both potential institutional conflicts and potential individual conflicts is now a minimum among best practice standards.

Institutional conflicts arise from financial or associational interests held by the institutional entity itself, directly or indirectly, in or with a sponsor of research, or in or with an entity that has a direct or indirect financial interest in the sponsor or otherwise stands to benefit from the results of the research study ("Institutional Interest"). They also arise from individual financial or associational interests that are held by an "institutional official," directly or indirectly, in or with the sponsor or such other outside entity and that are imputed to the institution because of decision-making authority the individual may hold over research matters (e.g., a member of the board of directors or a board committee, member of the executive team, clinical department chair, or member of the IRB ("Imputed Interest")). As discussed further below, the information research conflict disclosure questionnaires traditionally have elicited likely will be insufficient to identify Institutional and Imputed Interests; therefore, a new approach is required to capture such information.

Rebuttable Presumption That an Interest Presents a Conflict of Interest. A rapidly growing trend is for policies on conflicts in research to establish a rebuttable presumption that certain types of interests are conflicts of interest that should preclude the holder's participation in the research unless compelling circumstances exist to the contrary. These typically include financial interests exceeding a certain dollar or value threshold and associational interests creating a fiduciary duty to a financial sponsor of research (e.g., membership on a board of directors or committee with board-delegated authority or upper management positions, even if no compensation or minimal compensation is received). Also, they have been geared toward Individual rather than Institutional Interests.

Variations exist with regard to the financial threshold used.⁵¹ Frequently, conflicts policies establish a lower threshold for interests in private companies or apply the presumption to all interests in private companies, and they prohibit ownership of stock or stock options in a company while conducting research on its behalf.⁵² Whatever financial thresholds or other factors the policy establishes for triggering the presumption, the same thresholds should not be extended to the disclosure forms used to implement the policy; the disclosure forms instead should seek information concerning interests of any type, amount or value.⁵³

The conflicts policy should assign to the conflicts committee itself the responsibility for supplementing the rebuttable presumption provisions of the policy with guidelines and criteria for determining whether compelling circumstances exist and for the development of conflict management plans for cases in which the conflicts committee concludes for a given study that they do.⁵⁴ While the committee can delegate certain aspects of these responsibilities, it should play an active role in fulfilling them; in all cases, the committee's final approval of guidelines and criteria should be required.

Sanctions for Noncompliance with the Policy

Sanctions for noncompliance with the research conflicts policy, particularly the provisions requiring complete, accurate, and timely

completion of the conflicts disclosure questionnaire on an annual and ongoing basis, clearly will enhance the enforceability and effectiveness of the policy. The sanctions should be significant and the institution must be willing to firmly and consistently enforce them. Ties to annual renewals of medical staff or faculty status can be effective, as can be suspension or termination of such status.

Uniformity for All Research Regardless of Funding Source

While room exists to apply certain requirements and best practice standards only to federally funded research, an organization should consider adopting or evolving quickly toward a conflicts policy that applies uniformly to all human subject research regardless of funding source.

Disclosure Process and Forms

The following are disclosure process and questionnaire reforms that should be considered sooner rather than later on an organization's phased conflict-of-interest reform work plan

Require disclosure by all members of the research team. Bias that affects the integrity of a study and subject safety can arise from financial and associational interests held by any member of a research team, not just principal investigators. Requiring all members of the team to make initial, annual, and ongoing disclosures and to participate in corresponding conflicts training programs is essential. Holding the principal investigator responsible for obtaining the disclosure forms from other members of the team should make change more manageable, but his or her responsibility should not relieve individual team members from the task of thoroughly and thoughtfully completing their own questionnaires and complying with plans developed to manage conflicts in a study. With this expansion of the pool of individuals obligated to disclose, it also will be important to encourage principal investigators to list as part of the research team in the study protocol only the names of individuals who will in fact play a meaningful role so that anyone who is listed is fully aware of their corresponding conflict disclosure obligations.

Require disclosure by Institutional Officials, regardless of whether they are part of the research team. Requiring Institutional Officials to complete research-related conflicts disclosures will be necessary to pick up potential Imputed Interests. The disclosure by Institutional Officials should be accomplished through the broader disclosure questionnaire used for board members, executive management, and other officers, rather than a study-specific disclosure form, but the broader questionnaire should include questions targeted to conflicts in research. If revising the broader disclosure process and tools to address institutional interests in research will not occur immediately or in the very near future, however, an organization should use the research study-specific disclosure as the vehicle for accomplishing this reform in the short term.

Focus on disclosure of Interests, Not Conflicts of Interest. Conflict disclosure questionnaires traditionally have called on the disclosing party to make judgments as to whether a conflict arises from an interest, using questions such as "do you have an interest that gives rise to a conflict of interest with regard to the study sponsor." A better approach is to avoid questions that call on the disclosing party to be the judge of whether a financial or associational interest gives rise to conflict or appearance of conflict. Avoiding questions that are overly burdensome or intrusive, however, will be a challenge; an electronic disclosure process and accompanying database of entities to be considered by the disclosing party will facilitate the ability to overcome that challenge.

Abandon use of financial thresholds as a trigger for disclosure. The PHS defines a "significant financial interest" as (a) equity interests valued at \$10,000 or more, or 5 percent or more in ownership interest in the sponsor, or (b) a salary or consulting arrangements that are expected to reach or exceed \$10,000 in the next year. Use of this and similar thresholds on conflict disclosure forms has been the prevailing approach. Organizations should now consider eliminating such financial thresholds from the disclosure form in favor of requiring disclosure of interests of any value and using the thresholds instead as a criterion or guideline for the conflict-of-interest committee to use in assessing whether an interest gives rise to a conflict.

Emphasize the need for redisclosure of interests from year-to-year and for immediate disclosure as interests change between annual disclosure filings. Inadequate disclosure can occur when individuals assume that interests disclosed on a prior year's conflicts questionnaire need not be redisclosed on the current year's form even if the individual still holds the interests. Explicit instructions to this effect on the face of the disclosure form can reduce the occurrence of such misunderstandings. Providing individuals with a copy of his or her disclosure form from the previous year will help to assure cumulative disclosures of currently held interests from year-to-year and can highlight where significant changes have occurred; and an electronic disclosure system can reduce the burden of including this additional step in the process. The face of the form also should include an explicit reminder that an individual must disclose changes in such interests and new interests that arise between annual disclosures.

Manage the risk of multiple disclosure forms. An investigator or other research team member may be presented with conflict

disclosure forms from various sources (e.g., IRB, FDA, site institution, journal, or other publisher) at different times in the course of a study. These forms often vary in their approach and in the nature of the information they seek. Using a single form is not possible. Conflicts policies, procedures, and training programs should seek to prevent individuals from assuming that completing one of the various forms satisfies the need to complete the others and from providing inconsistent information from form to form.

Supplement individual disclosure forms with internal administrative procedures and forms for identifying and tracking Institutional Interests. A reliable means of identifying and assessing conflicts must include tools to identify all types of potential conflicts, Individual, Institutional, and Imputed. By their very nature, conflicts disclosure forms seek information concerning only Individual Interests that can give rise to an Individual Conflict or an Imputed Conflict; such forms will not identify financial and associational interests held by an institutional site as an entity. Therefore, an important additional step in revising research conflicts policy and procedures to achieve best practice standards is to supplement the use of individual disclosure forms with an internal administrative review of direct or indirect, financial, or associational interests held by the institution itself. Examples include equity interests in research sponsors and investments held in entities or funds in which research sponsors are co-investors. At a minimum, policies and procedures should expressly require such a review; an organization may also wish to develop a template to facilitate and document taking this step. Developing and maintaining an ongoing catalogue of such interests will significantly expedite this process, particularly if the catalogue is maintained in electronic form. Even in the absence of a centralized catalogue of such interests, however, organizations will be expected to undertake such a review and no other disclosure step or tool will be an adequate substitute.

Allocating Responsibility for Conflicts of Interest in Research

Institutions should assume responsibility for conflicts of interest in research conducted at their sites. If an IRB conducts a conflicts review, it likely will focus only on potential conflicts arising from individual interests of principal investigators and co-investigators. Some IRBs do not address conflicts of interest at all. Those that do will not have the necessary infrastructure to address potential Institutional and Imputed conflicts. Neither current federal requirements nor emerging best practices require IRBs to assume more responsibility for conflicts. Rather, they call for creation of an institutional committee separate from an IRB as the vehicle for identifying, assessing, and managing conflicts.

At a minimum, therefore, institutions serving as sites for research (regardless of the research funding source) must assume primary responsibility for conflicts, particularly Institutional and Imputed Conflicts. In most cases, the responsibility should reside in a committee of the board of directors. Creating a research conflicts subcommittee of another board committee may be the appropriate vehicle. Having the committee report directly to the board meets a higher standard. The driving consideration in choosing the appropriate committee should be what will be most effective within the overall governance structure, taking into account relevant factors such as the pool of available expertise and other resources. The membership of the chosen committee must be independent and include individuals with expertise appropriate for addressing research conflicts. Including a "community" representative who will focus primarily on subject safety is highly recommended. Conflicts policies and procedures should establish clear, mandatory lines of communication between the institution's conflicts committee and the applicable IRB or IRBs. As the institution's research program evolves and changes, it should periodically re-evaluate the effectiveness of the then-current committee structure.

Delegation by the Committee on Conflicts of Interest in Research. The committee responsible for research conflicts should retain ultimate authority and accountability for identifying, assessing, and eliminating or managing such conflicts. Delegation of certain tasks (e.g., initial review of conflicts disclosures, assessment of interests that fall within certain parameters, initial preparation of conflict management plans) to administrative officials (e.g., compliance officer, internal legal counsel, research administrators) will be necessary to avoid overburdening the committee and causing delay in and disruption to research. However, the committee should carefully develop and approve guidelines and tools for use by those to whom it has delegated such responsibilities.

Managing Conflicts of Interest in Research

Any conflicts program reform effort must place a high priority on the improvements in the development, implementation, and enforcement of conflict management plans ("CMPs").

The approach and contents of a CMP will vary depending upon the applicable facts and circumstances (e.g., the nature of the interest, the design of the study, whether the conflict is identified prior to or in the course of the study). It may be difficult to develop a template CMP that will be appropriate for all, or even the majority, of the situations that arise. Development of guidelines containing questions and possible plan elements is a useful alternative. It also may be possible to prescribe by policy the inclusion of certain essential elements in all CMPs, such as obligating the principal investigators to make periodic written reports to the conflicts committee concerning compliance with the plan, requiring that the plan be communicated to the IRB and some or all other members of the research team, and requiring that certain information concerning the conflict be disclosed in

writing to the study subjects in the written informed consent

Disclosure in the informed consent is becoming the rule, rather than the exception. Different views exist, however, concerning the nature and extent of the information that should be provided. As with other important elements of the informed consent, the focus of the debate is on the somewhat competing needs of informing the subject and avoiding confusion. Some institutions require only a statement that an investigator (unnamed) has a conflict of interest. Other institutions name the interested investigator, or the institution itself in the case of an institutional conflict of interest. Still others provide detail concerning the type and value of the interest. Best practices standards are still evolving on this front. Little doubt remains, however, that disclosure in the informed consent alone is unlikely to suffice in most cases as adequate protection against the risk of harm to subjects and the threat to research integrity arising from actual or apparent conflicts of interest.

An Effective Research Conflicts Program Requires a Multi-Disciplinary Perspective and Approach

The increased focus on Institutional and Imputed Conflicts requires consideration of the potential for conflicts in research when making decisions other than whether to participate in certain research. Examples of the many other types of decisions include making investments in pharmaceutical or device start-up ventures, investments in funds that finance such start-up ventures, accepting a large charitable donation from an industry entity that engages in health care research, and entering into a major vendor relationship with such an industry entity. An important step in the evaluation of such transactions or relationships is to determine whether the institution has in the past engaged, is currently engaged, or has plans in the future to engage, in research studies funded by the other entity involved. This will require, among other things, maintaining an ongoing list of past, present, and future research relationships that can be used for such cross-functional conflicts checks; maintaining an electronic, searchable database containing such a list will certainly enhance and expedite this task.

At the same time, however, emerging best practices are calling for separation of the research affairs and financial affairs (e.g., investments, fundraising, purchasing, commercialization, and strategic ventures) of an institution. The result is a need to establish "firewalls" to restrict communication that can inject bias into the decisionmaking process on either side of the wall.

Clearly, the firewalls cannot be structured in a way that prevents a finance or investment committee of the board from having the information needed to identify research relationships that create actual or apparent conflicts. Striking a balance between these competing practices will be both essential and challenging. Use of an intermediary such as the compliance officer, general counsel, or the conflicts committee may be an effective means of meeting both these needs. Other possible measures include allowing information to flow in one direction but not another depending upon where the greater risk of bias lies, and restricting the nature and extent of the information shared with the decisionmakers.

CONCLUSION

Federal regulations pertaining to conflicts of interest in research are a mere floor for research conflicts compliance programs; they lag far behind emerging best practice standards. The public, the courts, the media, and industry trade associations have sent the clear and consistent message that simply meeting the requirements of those regulations no longer will be adequate. Institutions serving as sites for human research studies must respond by assuming significant responsibility for identifying, assessing, and managing conflicts of interest for research conducted in their facilities and quickly adapting their governance structure and conflict-of-interest policies and procedures to emerging best practices standards.

¹ See, e.g., *Gelsing v. Trustees of U. Penn.*, No. 001885 (Pa. C.P., settled 11/2/00); *Wright v. Fred Hutchison Cancer Ctr*, Wash. Super Ct (No. 01-2-008376, complaint filed 3/26/01; available at <http://www.sskrplaw.com/gene/wright/complaint1.html>); and *Quinn v. Abiomed Inc. et al.* (Pa. Ct. Com. Pl., No. 001524, complaint filed 10/16/02), in which claims of common law misrepresentation and fraud were based in part on failure to disclose information on potential conflicts of interest that would have a bearing on a participants' decision to participate in a research study.

² See, e.g., Raha Mishra, "Harvard Medical Amends Policies: Rules for Faculty on Conflicts May Become a Model," *Boston Globe*, p. D1, 5/29/04.

³ A discussion of best practice standards for bench and animal research is outside the scope of this article

⁴ Certain state laws and ethical codes also address such conflicts of interest and must be taken into account in the development of internal policies and procedures for addressing potential conflicts of interest in research. A discussion of such laws and codes is outside the scope of this article. In addition, this article focuses on the laws and best practice standards for human subject research, not those relating to bench or animal research

⁵ PHS is part of the U.S. Department of Health and Human Services ("HHS") and is comprised of 8 agencies, including, among others, the National Institutes of Health ("NIH"), the Food and Drug Administration ("FDA"), the Indian Health Service, and the Centers for Disease Control and Prevention ("CDC")

⁶ 45 C.F.R. §46.103.

⁷ 42 C.F.R. §50.604(c)

⁸ 21 C.F.R. §54.1 *et seq*

⁹ "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection," 69 Fed. Reg. 26393, 5/12/04; available at: <http://www.hhs.gov/ohrp/humansubjects/finreltn/finalguid.pdf>.

¹⁰ 42 C.F.R. §§50.601, 50.602, 50.603

¹¹ 42 C.F.R. §50.604(a). The institution must provide these policies to each Investigator, subgrantee, contractor, or collaborator conducting research under the PHS award. The institution also must maintain a record of all financial disclosures and actions taken with respect to each such disclosed interest for at least three years from the date of submission of the final expenditure report, or where applicable, from such other dates as specified in 45 C.F.R. §74.53(b) 42 C.F.R. §50.604(e).

¹² 42 C.F.R. §§50.603, 50.604(c). Notably, this language is sufficiently broad to encompass interests held directly or indirectly in entities with an interest.

¹³ 42 C.F.R. §50.603.

¹⁴ 42 C.F.R. §50.603

¹⁵ 42 C.F.R. §50.603.

¹⁶ 42 C.F.R. §50.604(c)(2)

¹⁷ 42 C.F.R. §50.605(a).

¹⁸ 42 C.F.R. §50.605

¹⁹ Association of American Medical Colleges, *Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research* (1990); available at <http://www.aamc.org/>.

²⁰ 42 C.F.R. §50.604(g)(2)

²¹ 42 C.F.R. §50.604(g)(2).

²² 42 C.F.R. §50.606.

²³ Form PHS-398.

²⁴ "Financial Conflicts Of Interest And Research Objectivity: Issues For Investigators And Institutional Review Boards," NIH Notice OD-00-040, 6/5/00; available at <http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-00-040.html>. NIH has announced plans to overhaul its rules regarding conflicts of interest.

²⁵ In addition, the National Science Foundation published an *Investigator Financial Disclosure Policy* that requires grantee institutions employing more than 50 persons to maintain their own conflict-of-interest policies, to establish certain minimum requirements for those polices, and to require certifications from principal investigators, co-principal investigators, and authorized institutional representatives (59 Fed. Reg. 33308, 6/28/94)

²⁶ 21 C.F.R. §54.1 *et seq.*

²⁷ 21 C.F.R. §54.2(f).

²⁸ 21 C.F.R. §54.2(b).

²⁹ 21 C.F.R. §54.5(c).

³⁰ 21 C.F.R. §312.53 and 21 C.F.R. §812.43, respectively.

³¹ 21 C.F.R. Part 54.

³² 69 Fed. Reg. 26393, available at: <http://www.hhs.gov/ohrp/humansubjects/finreltn/finalguid.pdf>. This document replaced a previous draft guidance on the same topic issued on March 31, 2003 (68 Fed. Reg. 15456), which replaced the much more detailed draft guidance published in January 2001 (available at: <http://www.hhs.gov/ohrp/humansubjects/finreltn/finguid.htm>). See also, the comments to the January 2001 draft guidance submitted by the National Human Research Protections Advisory Committee ("NHRPAC," 8/23/01), which provide various suggested conflict-of-interest approaches and are available at: <http://www.hhs.gov/ohrp/nhrpac/documents/aug01a.pdf> (NHRPAC had the duty and responsibility of advising the director of the HHS Office for Human Research Protections ("OHRP") on significant issues in the regulations and oversight of human subjects research. Its charter expired in July 2002. The Secretary's Advisory Committee on Human Subject Protections ("SACHRP") was chartered on Oct. 1, 2002)

³³ See, *Biomedical Research: HHS Direction Needed to Address Financial Conflicts of Interest*, Government Accountability Office Report No. GAO-02-89 (12/18/01); *Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research*, DHHS Office of Inspector General ("OIG") Report OEI-01-97-00195 (June 2000) (which includes as appendices two FDA information sheets related to recruitment issues titled "Recruiting Study Subjects" and "Payment to Research Subjects"); *Recruiting Human Subjects: Sample Guidelines for Practice*, OIG Report OEI-01-97-00196 (June 2000); *FDA Oversight of Clinical Investigators*, OIG Report OEI-05-99-00350 (June 2000); *Protecting Human Research Subjects: Status of Recommendations*, OIG Report OEI-01-97-00197 (August 2000); Letter from Senator Charles Grassley, chairman of the Senate Committee on Finance, to Daniel Levinson, DHHS Inspector General, requesting the OIG to review the issues identified in the *Bloomberg Markets* report entitled, "Big Pharma's Shameful Secret" (December 2005) and provide the federal agencies with jurisdiction over clinical research with recommendations relating to strengthening protections of human subject (e.g., increased FDA oversight), <http://www.bloomberg.com/specialreport/bfm45c.pdf#search=%22%22Inspector%20general%20Levinson%22%20medicare%20and%20medicaid%20%22among%20other%20matters%22%22>; DHHS OIG, "Solicitation of Information and Recommendations for Developing Compliance Program Guidance for Recipients of NIH Research Grants," 68 Fed. Reg. 52783 (9/5/03).

³⁴ 69 Fed. Reg. 26393, 5/12/04.

³⁵ 31 U.S.C. §3729, *et seq.*

³⁶ See, e.g., *United States ex rel. Cantekin v. University of Pittsburgh*, 192 F.3d 402 (3rd Cir. 1999), involving liability under the FCA for a professor conducting medical research based on false certifications made on a PHS 398 grant application with regard to conflicts of interest in the research. See also various media reports cited in footnote 43.

³⁷ "Public Health Service Policies on Research Misconduct," 42 C.F.R. Part 93, which embody the new PHS rules on research misconduct and supersede the former regulations, "Responsibilities of Awardees and Applicant Institutions for Dealing with and Reporting Possible Misconduct in Science," codified at 42 C.F.R. Part 50, subpart A. See also, the Web page for the DHHS Office of Research Integrity at <http://ori.dhhs.gov/> for more information about research misconduct.

³⁸ A recent survey conducted by an independent scientific team reports that one-third of American biomedical scientists have self-reported some level of scientific misconduct. "Surveyed Scientists Admit Misconduct," *Boston Globe*, 6/9/05.

³⁹ 42 C.F.R. §93.103.

⁴⁰ David Hoffman, Assistant U.S. Attorney for the Eastern District of Pennsylvania, quoted in "Medical Research: Federal Prosecutor Warns Researchers on Legal Dangers of Conflicts of Interest," *BNA Health Care Daily Report* (3/21/01).

⁴¹ See *Moore v. Regents of University of California*, 51 Cal.3d 120, 133 (1990).

⁴² *Gelsinger v. Trustees of Univ. of Penn.*, No. 001885, Pa. Ct. of Com. Pl. (2000). The case was settled for an undisclosed amount on Nov. 2, 2000.

⁴³ Following the filing of this and other related lawsuits, the Fred Hutchison Center appointed a patient protection committee to review the center's policies and practices. The committee recommended that the center revise its policies to clearly prohibit arrangements between members of its staff and companies that could benefit from trials conducted by the center.

⁴⁴ *Quinn v. Abiomed Inc.*, Pa. Ct. Com. Pl., No. 001524, complaint filed 10/16/02.

⁴⁵ *Hamlet v. Fradin*, N.C. Sup. Ct., No. 03 CVS 1161 (complaint filed in July 2003), is available at: <http://www.sskrplaw.com/gene/hamletcomplaint.pdf>.

⁴⁶ See, e.g., Barry Meier, "Implant Program for Heart Device Was a Sales Spur," *New York Times*, 10/27/05 (focusing on a device manufacturer's payments to cardiologists of \$1,000 per implant of the manufacturer's cardiac device in connection with what could be characterized as post-market product research and evaluation and nondisclosure of such payments to at least some of the patients involved); Reed Abelson, "Possible Conflicts for Doctors are Seen on Medical Devices," *New York Times*, 10/22/05 (suggesting a connection between (1) frequent use of a particular artificial knee implant by a university physician, and (2) the physician's receipt from the implant manufacturer of advance royalty payments and payments under his contract to provide consultation on product design and promoting and educating other surgeons; and suggesting more generally that other financial arrangements between physicians and manufacturers can serve as incentives for use of a given device such as royalties, payment of expenses for educational conferences, fellowships, unrestricted grants, and ownership of manufacturer stock directly or through a research foundation); David Armstrong, "How a Famed Hospital Invests In Device It Uses and Promotes," *The Wall Street Journal*, 12/12/05, and David Armstrong, "Cleveland Clinic Had Ties to Maker of Faulted Device," *The Wall Street Journal*, 12/16/05 (focusing on direct and indirect interests held by a health care institution and its institutional officials both directly and indirectly in industry entities that manufacture products purchased by and that sponsor research conducted at the institution); Reed Abelson, "Cleveland Clinic Moves to Fight Conflicts of Interest," *The New York Times*, 3/10/06; Tony Leys, "Methodist Settles Suit Alleging Kickbacks, Denies Wrongdoing," *Des Moines Register*, 2/9/06 (reporting on settlement of patient lawsuit alleging that a medical center's executives pressured physicians to use a specific brand of pacemaker in order to receive substantial rebates from the device manufacturer); "Surveyed Scientists Admit Misconduct," *Boston Globe*, 6/9/05; Michael Romano, "Fighting Graft--It's Academic," *Modern Healthcare*, 1/30/06; Troyen

A. Brennan, M.D., M.P.H., et al., "Health Industry Practices that Create Conflicts of Interest--A Policy Proposal for Academic Medical Centers," *Journal of the American Medical Association*, 1/25/06; and Reed Abelson, "Whistle-Blower Suit Says Device Maker Generously Rewards Doctors," *The New York Times*, 1/24/06.

⁴⁷ Association of American Universities ("AAU"), "Report on Individual and Institutional Financial Conflicts of Interest," <http://www.aau.edu/research/COI.01.pdf> (October 2001); Association of American Medical Colleges ("AAMC"), "Protecting Subjects, Preserving Trust, Promoting Progress: Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research," <http://www.aamc.org/research/coi/firstreport.pdf> (December 2001); AAMC, "Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research," <http://www.aamc.org/research/coi/2002coireport.pdf> (October 2002); AAMC, "U.S. Medical School Policies on Individual Financial Conflicts of Interest: Results of an AAMC Survey," <http://www.aamc.org/research/coi/coireresults2003.pdf> (September 2004); American Medical Association ("AMA"), Council on Ethical and Judicial Affairs June 2001 Report 2 A-01, "Ethical Considerations in International Research," http://www.ama-assn.org/ama1/pub/upload/mm/369/ceja_2a01.pdf, and Ethics Opinion E-8.0315, "Managing Conflicts of Interest in the Conduct of Clinical Trials," <http://www.ama-assn.org/ama/pub/category/8471.html>; Pharmaceutical Research and Manufacturers of America ("PhRMA"), "Code on Interactions With Healthcare Professionals," <http://www.phrma.org/files/PhRMA%20Code.pdf>; Advanced Medical Technology Association ("ADVAMED"), "Code of Ethics on Interactions With Health Care Professionals," http://www.advamed.org/publicdocs/coe_with_faqs_4-15-05.pdf

⁴⁸ 42 C.F.R. §50.605(a)

⁴⁹ For example, in the revisions it made to its faculty conflicts-of-interest policy in May 2004.

⁵⁰ For example, some organizations have defined "Immediate Family" to include a research team member's spouse, domestic partner, sibling, grandparent, child, grandchild, or great grandchild if (a) the individual lives in the research team member's household, (b) the research team member manages the financial affairs of the individual, or (c) the research team member is aware without special inquiry that the family member holds an interest covered by the disclosure obligations.

⁵¹ In May 2004, for example, Harvard Medical School increased the amount of stock faculty members can own (from \$20,000 to \$30,000) in, and the amount of consulting and other fees they can receive (from \$10,000 to \$20,000) from, public firms utilizing their research. However, the policy prohibits faculty members from owning any stock in companies with which they have ongoing research collaborations and they cannot own stock in private companies related to their research. Raja Mishra, "Harvard Medical Amends Policies: Rules for Faculty on Conflicts May Become a Model," *Boston Globe*, p. D1, 5/29/04.

⁵² *Id.*

⁵³ See discussion below.

⁵⁴ See discussion below. 

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