
Financial Conflict of Interest in Medical Research: Overview and Analysis of Federal and State Controls

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Executive Summary

Over the past two decades, increasing collaboration between industry and academic research institutions has given rise to exciting new opportunities for medical researchers and the medical technology community in general. These opportunities have in turn generated important medical advances and new policy challenges. Financial conflict of interest, both at the individual and institutional levels, is among the key issues resulting from this new medical research environment. To solidify existing collaborative paradigms and lay the foundation for future benefits from the academia-industry partnership, financial conflict of interest must be successfully addressed.

In its broadest sense, a conflict of interest in medical research occurs when an external relationship, whether financial or not, influences, or appears to influence, an individual's or institution's attitude or behavior toward particular

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research, creating the potential for compromised research results or, in the case of clinical trials, harm to human research subjects. Financial conflict of interest is a narrower set of conflicts encompassing only those external relationships that are financial in nature. Comprising the financial subset are various types of external relationships, including equity holdings, ownership interests, patent agreements, and royalty arrangements. These types of financial relationships can further be distinguished according to the actual monetary amount of the relationship at issue.

Due in part to their use of varying financial conflict definitions, the current federal controls governing financial conflict of interest form an incomplete patchwork of uncoordinated efforts to protect the integrity of medical research and the safety of medical research participants. As a result, the regulations are not uniform in scope, applicability, or substance, and often result in considerable confusion on the part of those required to comply with them. They include:

- Federal Policy for the Protection of Human Subjects (“The Common Rule”). Promulgated by the Department of Health and Human Services (HHS) in 1991, the Common Rule represents the core of current federal regulations designed to protect human research subjects. Adopted by seventeen federal agencies, they apply to all federally funded research involving human subjects. The Rule requires informed consent for experimental subjects and grants IRB authority to oversee clinical experiments. Importantly, the regulations do not explicitly address investigator or institutional financial conflicts.
- Public Health Service (PHS) Regulations. Promulgated in 1995, these regulations explicitly address financial conflict of interest and are applicable to every institution applying for PHS grants. Intended to protect research objectivity through the management, reduction, or elimination of financial conflicts, they require institutions to maintain and enforce written conflict policies, as well as designate an official to review conflict disclosure statements. The regulations provide a broad definition of financial conflict of interest, which exists when a “significant financial interests” (defined as anything of monetary value including salary and intellectual property rights exceeding \$10,000 in the aggregate, and equity interests exceeding the \$10,000 or 5% ownership interest threshold) directly or significantly affects the PHS-funded research. Notably, institutions are

left to decide whether the significant financial interest constitutes a reportable conflict of interest and the type of management employed.

- Food and Drug Administration’s (FDA) Disclosure Regulations. Effective since 1999, the FDA regulations require sponsors of clinical studies undertaken in support of marketing approval applications to disclose specific types of financial arrangements, with a focus on maintaining data integrity. Where a study investigator or institution receives payments over \$25,000 from the sponsor, holds equity over \$50,000 in the sponsor, or has proprietary interests in the tested product, the sponsor must report these interests in its application to the FDA along with steps taken to minimize potential bias. Notably, disclosure is made only after the submission of data, effectively resulting in an ex post facto review by FDA.
- Department of Health and Human Services Draft Interim Guidance. Released in May of 2000, the draft guidance is directed at institutions, investigators, IRBs, and the informed consent process. Although the guidance does not carry the legal force of regulation, it provides insight into possible future initiatives. As a general rule, the guidance counsels against the direct participation of interested investigators in trials that could be impacted by conflicts. It suggests broader communication between IRBs, conflict of interest committees, and institutions, and promotes educational initiatives for investigators and IRB members. With respect to informed consent, the guidance recommends research subjects be informed of financial interests through the consent form whenever it is deemed to be material to an informed decision.

In addition to federal controls, state courts have addressed conflict of interest in the setting of informed consent. Specifically, in *Moore v. Regents of the University of California*, the court held informed consent includes a physician’s duty to reveal potential conflicts to patients under their care. While state court decisions are influential on court decisions nationwide, there has not been a similar interpretation at the federal regulatory level.

Together, federal and state controls on financial conflict of interest form an overlapping, incomplete, and occasionally conflicting message to investigators and institutions involved in partnerships with industry, making compliance difficult and creating the potential for considerable variation in actual policy application at the local level.

I. Introduction

Since passage of the Bayh-Dole Act in 1980,¹ medical research collaborations between private industry and academic research institutions have increased substantially. Accompanying this dramatic growth in collaborations is a complex web of financial relationships among industry leaders, academic institutions, and institutional investigators. These relationships have created important incentives for the development of new technologies, but they have also raised concerning issues, most notably financial conflict of interest, for both individual investigators and academic institutions.

Conflict of interest in medical research exist when external relationships influence, or appear to influence, an individual's or institution's attitude or behavior toward particular research. Financial conflicts of interest, as a subset of conflicts of interest, encompass only those external relationships that are financial in nature. Whether real or perceived, such conflicts have the potential to undermine the integrity of medical research results, threaten the safety of research subjects, and diminish public trust in academic medical research.

Considering the present and future public benefit of academia-industry collaborations, real or perceived financial conflicts of interest must be thoughtfully addressed. To understand how the academic medical community can approach financial conflict of interest issues constructively, it is essential to have an understanding of the environment within which medical research is conducted in terms of the Bayh-Dole Act and the federal regulations governing financial conflicts.

II. The Medical Research Environment and Financial Conflict of Interest

Today's medical research is conducted in an environment shaped to a large degree by the Bayh-Dole Act of 1980.² Prior to this legislation, ownership of intellectual property resulting from federally funded research automatically vested in the government itself. As the government largely lacked mechanisms to transfer this intellectual property to industry, discoveries often languished with little or no benefit to the public. The Bayh-Dole Act shifted this paradigm, transferring ownership of the intellectual property resulting from federally funded research to the private or non-profit entities conducting the research. In effect, the Act used the patent system to promote the broad dissemination of potentially useful discoveries.³ As a result, the Act

enabled universities, non-profit corporations and small businesses to commercialize federally funded inventions and new technologies by giving these entities the power to patent the products of their work.⁴

The Bayh-Dole Act produced a dramatic increase in medical research funding, collaborative research relationships, university-issued patents, and start-up companies formed from university licensing agreements. For example, industry funding of medical research increased from \$1.5 billion in 1980 to \$22.4 billion in 2000.⁵ The number of patents awarded from research conducted at universities increased from approximately 250 annually in 1980 to 4,800 in 1998.⁶ Furthermore, over 2,200 new companies have been formed around the licensing of these inventions by universities.⁷

Accompanying the dramatic changes within the medical research environment were complex financial relationships that have in turn given rise to real and perceived financial conflicts of interest. These financial conflicts can exist on two levels: the individual level and the institutional level.

Individual financial conflicts typically occur when a faculty member of an academic institution, acting as the principle investigator for research sponsored by Company X, has an external financial relationship with Company X, through equity holdings or ownership interests, for example. This creates a situation whereby the results of the research may affect the investigator's personal financial holdings with Company X. The result is a financial conflict that may compromise the investigator's professional judgement through bias in the conduct of the research or the reporting of research results.

Institutional financial conflicts occur when the institution, or an institutional official who has the authority to make decisions on behalf of the institution, has a financial relationship with an outside entity that may influence its position with respect to the review or oversight of research conducted at the institution. For example, a financial conflict of interest exists when an institution, or an official of the institution, owns stock in Company X, when Company X is financially invested in an institutional faculty member's research. In this scenario, the institution's (or officer's) financial potential is tied to the outcome of the faculty member's research for Company X. The result is a conflict that may compromise the appropriateness of institutional decisions regarding that particular research.

Whether or not the existence of individual or institutional financial conflicts are a necessary evil of the current medical research environment, financial conflict of interest is a key issue tied to the future success of academia-industry partnerships. Responding to public concerns regarding research integrity and human subject safety, the federal government has issued various regulations and guidance documents.

III. Current Controls of Financial Conflict of Interest

Federal regulations developed to address the real or apparent biases that may result from financial conflicts form the current framework governing financial conflict of interest. Each regulation differs in its focus and definition of what constitutes a financial conflict, essentially creating a patchwork of regulations, some designed to protect the integrity of research results and other for the safety of human research participants. These federal controls consist of the Common Rule, the Public Health Service (PHS) regulations, and the Food and Drug Administration's (FDA) disclosure regulations. A draft guidance document issued by the Department of Health and Human Services (HHS), although not law, provides a glimpse into possible future federal initiatives. It is important to note that, due to their lack of comprehensiveness and uniformity in scope, applicability and substance, the federal regulations leave certain types of research unregulated, such as privately funded research where FDA approval is not sought.

A. Federal Controls

1. The Common Rule

In 1991, the Department of Health and Human Services (HHS), under the auspices of the National Institutes of Health (NIH) and its Office for Protection of Research Risks (OPRR),⁸ promulgated the Federal Policy for the Protection of Human Subjects, also known as the "Common Rule."⁹ The Common Rule comprises the first section of a series of regulations referred to as the Protection of Human Subjects and represents the core of current federal regulations designed to protect human research subjects.¹⁰ Adopted by seventeen federal agencies, the policy governs all federally funded research involving human subjects.^{11 12} The Office of Human Research Protection (OHRP) is the office responsible for implementation and enforcement of the regulations.¹³

The Common Rule does exempt from its requirements certain forms of human subject research. Specific exemptions exist for studies on education instructional strategies, use of educational tests or evaluations of public benefit programs.¹⁴ For example, research conducted in a classroom setting for the purpose of evaluating the effectiveness of instructional techniques would likely fall outside the scope of the federal policy.¹⁵ In addition to these exemptions, the Common Rule provides federal department or agency heads with the authority to waive the federal policy, in whole or in part, for particular research activities.¹⁶

The Common Rule is comprised of two separate, but equally important provisions: an informed consent requirement¹⁷ and the operational authority granted to Institutional Review Boards (IRBs). The consent requirement requires investigators to obtain the legally effective informed consent of all human research subjects,¹⁸ providing a list of elements investigators must satisfy in order to obtain such consent.¹⁹ For example, in seeking the consent of a research subject, an investigator must explain the purpose of the research and describe any reasonably foreseeable risks.²⁰

The second main provision governs IRB operational authority, charging IRB with the responsibility for determining whether investigators have satisfied the elements of consent procurement.²¹ IRBs are required to ensure that all material information to obtain a potential participant's consent is explained in clear, understandable language.²² In addition, the Common Rule charges IRBs with protecting the rights of human subjects throughout the duration of the research cycle. IRBs have the authority to review, modify and suspend research activities that do not conform to the Common Rule regulations.²³

The significance and import of the informed consent and IRB provisions notwithstanding, what is most striking about the Common Rule is what is lacking, namely provisions addressing financial conflict of interest for investigators and institutions conducting medical research with human subjects. The Common Rule does not direct investigators to disclose financial conflicts of interest under the informed consent requirement, nor does it require IRBs to consider financial conflicts of interest when reviewing research protocols. The regulations do address general conflicts of interest at the IRB level, namely in IRB research protocol review and IRB board membership are addressed. Specifically, IRB members may not participate in the review of

research projects when a “conflicting interest” exists.²⁴ Similarly, the regulations require at least one IRB member to be unaffiliated with the participating institution.²⁵ Although these two preceding provisions may theoretically deter financial conflicts of interest at the IRB level, the regulations themselves do not indicate a specific intent to control such conflicts at the investigator or institutional levels.

2. Public Health Service Regulations

The Public Health Service (PHS) regulations comprise a second type of federal control governing financial conflicts of interest in medical research. Promulgated in 1995 by the Public Health Service and HHS Office of the Secretary, the goal of the PHS regulations is to promote objectivity in research, targeting those institutions applying for PHS grants or cooperative agreements.²⁶ Under the broad definition provided in the PHS regulations, a conflict of interest exists when it is determined that, “a Significant Financial Interest could directly and significantly affect the design, conduct, or reporting of the PHS-funded research.”²⁷

The PHS regulations require institutions to satisfy four basic requirements as a requisite to receiving PHS funds: (1) maintain a written conflict of interest policy and enforce said policy;²⁸ (2) inform research investigators of the institution’s policy on conflicts of interest, the investigator’s reporting responsibilities, and other applicable federal regulations;²⁹ (3) designate an official to review financial disclosure statements of participating investigators;³⁰ and (4) report the existence of any financial conflict of interest to the grantor agency with an assurance from the institution that the conflict has been managed, reduced or eliminated.³¹

Pursuant to the PHS regulations, investigators participating in PHS-funded research are required to submit financial disclosure statements to the institution regarding any “significant financial interests” held by the investigator, his or her spouse, and dependent children.³² The regulations define significant financial interests as 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),” where salary and intellectual property rights exceed \$10,000 in the aggregate over a twelve month period, and where equity interests exceed \$10,000 or a 5% ownership interest.³³

Notably, the definition of significant financial interests does not include such financial interests as salary or royalties received from the applicant institution, income from lectures sponsored by nonprofit entities,³⁴ or ownership interests in the institution, if the institution is an applicant under the Small Business Innovation Research (SBIR) program.³⁵

Following investigator disclosure of any significant financial interests, institutions determine whether the financial interest of the investigator could affect the design, conduct, or reporting of the research in question.³⁶ In addition, the institution determines the form and degree of management employed for those significant financial interests that it deems to constitute a financial conflict.

Mechanisms, such as conditions or restrictions that may be appropriate to employ in a conflict situation in order to manage financial conflicts are provided in the regulations. Some examples include: public disclosure of the financial conflicts; monitoring of the research by independent reviewers; modification of the research protocol; removal of investigators from participation in all or part of the research; divestiture of the conflicting interest; and severance of the conflicting relationship.³⁷

The focus of the PHS regulations is on the management of financial conflicts of interest rather than a per se prohibition of such conflicts.³⁸ To that end, an applicant institution must provide its designated official with guidelines to identify financial conflicts of interest and “take such actions as necessary to ensure that such conflicting interests will be managed, reduced, or eliminated.”³⁹ Thus, while the management of financial conflicts of interests is a required responsibility among applicant institutions, designated officials retain significant discretion in determining when a significant financial interest constitutes a conflict requiring disclosure to the agency, as well as the degree of management ultimately employed in each case.

3. Food and Drug Administration Regulations

The existing Food and Drug Administration (FDA) regulations represent a combination of Common Rule concepts, as well as an explicit concern for financial conflict of interest. Although the FDA did not formally adopt the Common Rule following its promulgation, the agency did modify its regulations on human subject research in 1991 to conform to the largest extent possible with the Common Rule. Despite the modifications to conform, the Inspector

General of HHS submitted a management advisory report alleging a material weakness in the modified regulations, citing the agency's failure to establish a mechanism for gathering financial conflict of interest information from its applicants.⁴⁰ Although the agency determined that a material weakness did not exist, HHS did conclude that the FDA should address financial conflicts of interest through issuance of a rule. In 1998, the agency adopted new regulations addressing the issue of financial disclosures as it relates to clinical investigators, effective February 1999.⁴¹

FDA's financial disclosure rules apply to "covered" clinical studies which include, any study of a drug, biological product or medical device used to support premarket approval (PMA), reclassification petitions used to establish a product's efficacy or equivalency and studies in which a single investigator significantly contributes to the demonstration of safety.⁴² Thus, in addition to PMAs, every submission of a 510(k), product development protocol (PDP), and humanitarian device exemption (HDE) containing clinical data must include financial disclosure information.⁴³

Pursuant to FDA's financial disclosure regulations, applicants relying on covered studies are required to disclose the following types of financial interests or arrangements involving those clinical investigators who are not full- or part-time employees of the sponsor: (1) financial arrangements between the sponsor of the study and the investigator where the outcome of the study could increase the monetary value of the clinical investigator's financial interest such as explicit compensation agreements, equity interests in the sponsor, or royalty interests in the product;⁴⁴ (2) payments over \$25,000 made by the sponsor to the investigator or institution during a clinical trial or within one year of completion of the trial such as grants to fund ongoing research, compensation in the form of equipment, retainers for ongoing consultation, and honoraria;⁴⁵ (3) proprietary interests in the tested product including patent, trademark or copyright interests;⁴⁶ and (4) equity interests in the sponsor over \$50,000 in a publicly held sponsoring company during the trial or within one year of completion of the trial.⁴⁷ If none of the above exist, the regulations require certification of the absence of such financial interests.⁴⁸ In addition to the above disclosures, applicants must report any steps taken to minimize the potential for bias resulting from such financial interests, arrangements or payments.⁴⁹

Notably, FDA regulations require disclosure of financial conflicts of interest only after the applicable research has been performed. Once disclosed, the agency evaluates the information to discern its impact on the reliability of the study's data, taking into account the study's design.⁵⁰ Although the agency does not usually publicize disclosed financial conflicts of interest, it may reject data from studies if it determines that the disclosed financial interests could have adversely impacted the study.⁵¹ In addition, the agency also has the authority to audit an investigator's data, request that the applicant submit further analyses of the data, or request that the applicant submit additional studies.⁵²

4. Department of Health and Human Services, Draft Interim Guidance

In May 2000, then HHS Secretary Donna Shalala announced a series of initiatives to address human subject protection in clinical trials. Included among these initiatives was the development of agency guidance on financial conflicts of interest, largely in response to the death of 18-year old Jesse Gelsinger in a University of Pennsylvania gene therapy clinical trial in 1999.⁵³

Following this announcement, HHS hosted a conference on financial conflicts of interest, from which emerged the draft guidance *Financial Relationships in Clinical Research*.⁵⁴ In commentary prefacing the document, the agency explicitly states that despite PHS and FDA regulations, a uniform and comprehensive approach to the consideration of financial conflicts of interest in human research does not exist.⁵⁵ Specifically, the agency notes that neither the PHS nor FDA regulations address IRB responsibilities.⁵⁶ In response, HHS drafted guidance to address the role and responsibilities of IRBs, with the intent to "help IRBs, Clinical Investigators, and Institutions in carrying out their responsibilities to protect human subjects in research that they have under the Common Rule and the equivalent FDA regulations governing IRBs and Informed Consent."⁵⁷

The draft guidance defines a financial conflict of interest according to PHS regulations.⁵⁸ The guidance would require the collection of conflict of interest information from all investigators according to institutional policies and procedures, while further suggesting the possibility of collecting similar information typically required under FDA regulations for studies of FDA regulated articles.⁵⁹

In its attention to institutional roles and responsibilities, HHS cautions against the risk of

financial conflicts of interest when entering into business agreements with corporate entities. The guidance recommends establishing independent institutional Conflict of Interest (COI) committees and developing “special safeguards to maximally protect the scientific integrity of the study and research participants.”⁶⁰ In addition, the document suggests institutional financial relationships with the commercial sponsors be reported to the IRB.⁶¹ Included among these financial relationships are equity interests in the sponsor, payments to the institution beyond payments directly applicable to carrying out a particular protocol, and any funds transferred to the institution.⁶²

At the investigator level, HHS advises participation in educational and training programs on financial conflicts of interest. In addition, the guidance recommends institutional COI committees review all agreements between investigators and sponsors,⁶³ In situations where a conflict cannot be eliminated, the COI committee should share its recommendations with the IRB as to the management of the conflict.⁶⁴

In its treatment of IRB roles and responsibilities, HHS recommends institutions conduct annual reviews of potential financial conflicts among IRB members.⁶⁵ Specifically, the guidance states that institutional policies and procedures provide guidance on the management of potential and actual conflicts of interest.⁶⁶ Furthermore, the guidance suggests institutions require IRB member participation in educational programs on financial conflicts of interest.⁶⁷ In addition to annual reviews and educational programs, the guidance document recommends that the IRB Policy and Procedures Manual contain institutional and IRB financial conflict of interest policies.⁶⁸ Specifically, the guidance counsels that IRBs should have clear recusal procedures for members so as to eliminate their involvement in protocols that might raise potential or actual conflicts of interest.⁶⁹

IRB review of research protocols was another area addressed in the guidance, with particular attention given to informed consent. HHS recommends IRBs make final approval determinations when it has been determined that an institutional conflict is problematic.⁷⁰ Specifically, the IRB should consider whether conduct of the trial at that institution is appropriate, taking into consideration the feasibility of managing the conflict, including any necessary modifications to the protocol or consent form.⁷¹ In general, the guidance recommends that IRBs, whether institutional or independent, remain aware of funding arrangements for each reviewed protocol.⁷²

When a clinical investigator has a conflict that cannot be eliminated, the IRB would be responsible for considering modifications to the protocol, consent form, or “other approaches as appropriate.”⁷³ In making determinations, the guidance suggests that IRBs consider all elements that a designated institutional official would have to consider under PHS guidelines, as well as all FDA financial disclosure requirements.⁷⁴ In general, if a clinical investigator has a financial conflict of interest in the context of a trial, the investigator “should not be directly engaged in aspects of the trial that could be influenced by that conflict.”⁷⁵

In its delineation of informed consent, the guidance encourages IRBs to ensure that potential research participants are apprised of a study’s funding source as well as the payment arrangements for investigators. Information about funding and payment arrangements should be included in consent forms “whenever that information is considered to be material to the potential subjects’ decision-making process.”⁷⁶ When a conflict of interest exists, an IRB should consider taking “special measures” to modify the consent process, which “could include having a non-biased third party obtain consent, especially when conflicts could influence the tone or presentation of information during the consent process.”⁷⁷

B. Judicial Decisions and Informed Consent: *Moore v. Regents of the University of California (1990)*

Although numerous federal agencies have addressed conflicts of interest, the question of whether financial conflicts should be disclosed as part of the informed consent process remains, to some degree, unanswered. In a 1990 landmark case, *Moore v. Regents of the University of California*,⁷⁸ the Supreme Court of California reviewed the scope of the informed consent doctrine as it relates to conflict of interest. The court broadly interpreted such consent to include a physician’s duty to reveal potential conflicts of interests to patients who are under their care. While this decision is law in California and influential on courts nationwide, it is important to note that there has been no such interpretation or requirement at the federal regulatory level.

In *Moore*, the Supreme Court of California considered the breadth of the concept of informed consent and whether the doctrine includes a physician’s duty to reveal any research or potential financial conflicts of interests to a patient under their

care. The court concluded that adequate informed consent does indeed encompass a duty to disclose “personal interests unrelated to [a] patient’s health, whether research or economic, that may affect the physician’s professional judgment.”⁷⁹ The facts underlying the decision stemmed from plaintiff John Moore’s treatment for hairy-cell leukemia at UCLA Medical Center from 1976 to 1983. In 1976, Moore’s physician, Dr. David W. Golde, recommended the removal of Moore’s spleen, informing him that splenectomy was necessary to slow disease progression.⁸⁰ Moore signed a consent form authorizing the procedure based on Dr. Golde’s representations.

Prior to the splenectomy, Dr. Golde and Shirley G. Quan, a researcher employed by the Regents of the University of California, made arrangements to bring portions of Moore’s removed spleen to a separate research unit. Golde and Quan planned to conduct research on portions of Moore’s removed spleen. The research was unrelated to Moore’s medical care. Neither Golde nor Quan informed Moore of their intent to use his spleen for separate research activities, nor did they seek his permission.

Over the next several years, Moore returned to UCLA Medical Center on several occasions at the request of Golde, who represented the visits as necessary for Moore’s health. During each visit, Golde withdrew samples of blood, blood serum, skin, bone marrow aspirate, and sperm. Throughout this period of time, Golde and the other defendants conducted numerous research activities that they concealed from Moore. Most importantly, Dr. Golde established a cell line from Moore’s T-lymphocytes.⁸¹

In 1981, the Regents of the University of California applied for a patent on the cell line. According to university policy, the Regents, Dr. Golde, and Quan were to share in any royalties or profits arising out of the patent. The patent, issued in 1984, named the Regents of the University of California as the patent’s assignee, and Golde and Quan as inventors. With the patent obtained, Golde negotiated an agreement with the Genetics Institute, becoming a paid consultant for the Institute with the rights to 75,000 shares of common stock. In exchange for exclusive access to research performed on the cell line as well as products derived from it, the Genetics Institute agreed to pay Golde and the Regents a minimum of \$330,000 over three years, including a pro-rata share of Golde’s salary.⁸²

Ultimately, the Supreme Court of California found that Dr. Golde breached his fiduciary duty as a physician to Moore by concealing his research interests in Moore’s cells from the time he recommended the splenectomy procedure. Although the record did show that the operation itself was therapeutic, the court concluded that Dr. Golde was nevertheless obliged to disclose any additional research interests, even if they did not directly relate to his patient’s health.⁸³ By contrast, the court found that neither Quan nor the Regents of the University of California had failed to obtain Moore’s informed consent because neither of these defendants had a fiduciary duty to Moore. In making its decision, the court explicitly noted that the law does not prohibit a physician from conducting research within the same arena as he or she practices.⁸⁴

IV. Conclusion

An explosion of collaboration between industry and academic research institutions over the last two decades has given rise to new challenges, in particular effectively addressing conflict of interest to ensure human subject protection and research integrity. Current federal controls governing such conflicts, while extensive, are by no means comprehensive, uniform or coordinated. Similarly, state controls, primarily through the application of informed consent, fail to provide unambiguous guidance to investigators and institutions. Together, both federal and state controls provide a relative lack of prospective guidance as to what constitutes acceptable institutional conflict policy. The ultimate impact of this environment at the institutional level is the focus of Part II of this white paper.

TABLE 1
MAJOR FEDERAL REGULATION IMPACTING
FINANCIAL CONFLICT OF INTEREST IN MEDICAL RESEARCH

REGULATION	YEAR	OBJECTIVE	TYPE OF CONFLICTS	SCOPE (APPLIES TO...)	KEY MECHANISMS AND PROVISIONS
HHS – The Common Rule	1991	Protect human research subjects	IRB-level conflicts	All federally funded research involving human subjects	<ul style="list-style-type: none"> ◆ informed consent ◆ IRB authority ◆ no explicit financial conflict of interest provisions
PHS regulations	1995	Protect research objectivity	Individual financial conflicts	All institutions applying for PHS funding	<ul style="list-style-type: none"> ◆ broad definition of financial conflict includes any “significant financial interest” that could directly affect PHS-funded research ◆ requires institutions to maintain conflict policies ◆ investigator disclosure of “significant financial interests” to institutional official ◆ institutional discretion to decide when “significant financial interest” constitutes a financial conflict ◆ manage, reduce, or eliminate financial conflicts ◆ reporting to funding agency
FDA disclosure regulations	1999	Maintain data integrity	Individual financial conflicts	Sponsors submitting clinical data from “covered studies” for marketing approval	<ul style="list-style-type: none"> ◆ sponsor/applicant disclosure of investigator conflicts at time of submission ◆ clinical investigators must disclose: financial arrangements with sponsor; payments received from sponsor over \$25,000; proprietary interests in tested product; and equity interests in sponsor over \$50,000 in publicly-held sponsor.
HHS – Draft Interim Guidance	2000	Protect human research subjects	Individual and institutional financial conflicts	Provides guidance to IRBs, investigators, and institutions to carry out their responsibilities to protect human research subjects	<ul style="list-style-type: none"> ◆ increase communication between IRBs, conflict of interest committees and institutions ◆ educational initiatives ◆ disclosure of conflicts in informed consent documents when deemed “material” to an informed decision ◆ reporting of institutional financial conflicts to IRBs

References

¹ Amendments to the Patent and Trademark Act of 1980, 35 U.S.C. §§ 200-212 (2000).

² *See id.*

³ *Id.* at §200.

⁴ *Id.*

⁵ United States General Accounting Office, 2001. *Biomedical Research: HHS Direction Needed to Address Financial Conflicts of Interest*. Washington, D.C.: General Accounting Office.

⁶ *Id.*

⁷ The Bayh-Dole Act: A Guide to the Law and Implementing Regulations. Council on Government Relations, Sept. 1999, available at <<http://www.cogt.edu/bayh-dole.htm>> .

⁸ In 2000, OPRR was replaced by the Office for Human Research Protection (OHRP), which is currently overseen by the Secretary of HHS.

⁹ *See*, 45 C.F.R. § 46 (2000). The 1991 Common Rule draws from 1974 regulations issued by HHS, then known as the Department of Health, Education and Welfare (DHEW).

¹⁰ The Common Rule refers solely to Subpart A, which sets forth the basic federal policy for human research subject protection. *See generally*, 45 C.F.R. § 46. Subparts B, C and D delimit supplementary protections for fetuses and pregnant women, prisoners, and children, respectively. *See*, 45 C.F.R. at § 46.124; 45 C.F.R. at § 46.201-46.409.

¹¹ In addition to the Department of Health and Human Services, the following federal departments and agencies have incorporated the Common Rule regulations: The Agency for International Development; the Consumer Product Safety Commission; the Department of Commerce; the Department of Defense; the Department of Education; the Department of Energy; the Department of Housing and Urban Development; the Department of Justice; the Department of Transportation; the Department of Veterans' Affairs; the Environmental Protection Agency; the International Development Cooperation Agency; the National Aeronautics and Space Administration; the National Science Foundation; the United States Department of Agriculture.

¹² 45 C.F.R. at § 46.101(a).

¹³ *Id.* at § 46.

¹⁴ *Id.* at §46.101.

¹⁵ *Id.* at § 46.101(b)(1).

¹⁶ *Id.* at § 46.101(c) and (i).

¹⁷ The Common Rule is a recent successor of the Nuremberg Code (1947), one of the most historically significant documents in medical research ethics. *See*, The Nuremberg Code, available at <<http://ohrp.osophs.dhhs.gov/references/nurcode.htm>>. The Nuremberg Code's most notable and enduring addition to medical research standards was its insistence that "the voluntary consent of the human subject is absolutely essential." *Id.* Several decades later, this principle was refined and re-codified into the fundamental "informed consent" component of the Common Rule. *Id.*

¹⁸ 45 C.F.R. at § 46.116(a). The informed consent requirement also includes a catalogue of additional

elements that may be stipulated "when appropriate." *Id.* at § 46.116(b).

¹⁹ *Id.* at § 46.116.

²⁰ *Id.* at § 46.116(a)(1); 45 CFR at § 46.116(a)(2).

²¹ *Id.* at § 46.111.

²² *See id.* at § 46.116.

²³ *See id.* at § 46.113.

²⁴ *Id.* at § 46.107(e).

²⁵ *See id.* at § 46.107(d)

²⁶ 42 C.F.R. at § 50.602. The PHS regulations apply to individual investigators insofar as participating investigators apply for PHS grants through an institution. When an individual investigator rather than an institution applies for a PHS grant, assurance that any conflicting financial interest does not bias the research will be determined on a case-by-case basis.

²⁷ *Id.* § 50.603

²⁸ *Id.* at § 50.604(a).

²⁹ *Id.*

³⁰ *Id.* at § 50.604(b).

³¹ *Id.* § 50.

³² *Id.* § 50.604(c)(1).

³³ *Id.* § 50.603.

³⁴ *See id.* This section of the regulations includes a complete list of excluded financial interests.

³⁵ *Id.* Before the implementation of the final rule, some commentators criticized the exclusion of SBIR applicants from the financial disclosure rule. However, the SBIR exclusion was retained, as PHS believed that such ownership interests would be apparent to PHS funding agencies based on the application. 60 Fed. Reg. 35809, 35812 (July 11, 1995).

³⁶ 42 C.F.R. at § 50.605.

³⁷ *Id.*

³⁸ *Id.* § 50.605(a) (1999). *See also id.* at § 50.604(d) and *id.* at § 50.604(g)(1).

³⁹ *Id.* at § 50.604(d).

⁴⁰ *See* FDA guidance, "Financial Disclosure by Clinical Investigators," March 20, 2001, available at <<http://www.fda.gov/oc/guidance/financialdis.html>>.

⁴¹ *See*, 21 C.F.R. § 54 (2000) (stipulating rules of financial disclosure for clinical investigators). Although 21 C.F.R. § 54 is the primary regulation governing financial disclosures, the following other regulations contain financial disclosure requirements: § 312, § 314, § 320, § 330, § 601, § 807, § 812, § 814, and § 860.

⁴² *Id.* at § 54.3 and § 54.2(e).

⁴³ Phase I tolerance studies and most clinical pharmacology studies are not usually held to the financial disclosure requirements. *Id.* at § 54.2(e).

⁴⁴ *Id.* at § 54.2(f) and § 54.4(a)(3)(i).

⁴⁵ *Id.* at § 54.2(f) and § 54.4(a)(3)(ii).

⁴⁶ *Id.* at § 54.2(c) and § 54.4(a)(3)(iii).

⁴⁷ *Id.* at § 54.2(b) and § 54.4(a)(3)(iv).

⁴⁸ *Id.* at § 54.4(a)(1) and § 54.4(a)(3).

⁴⁹ *Id.* at § 54.4(a)(3)(v).

⁵⁰ *Id.* at § 54.5(a) and (b).

⁵¹ *Id.* at § 54.5(c)(4).

⁵² *Id.* at § 54.5(c)(1-3).

⁵³ Gelsinger was treated with an experimental virus to correct a genetic, but not harmful, liver disease. Both the

University of Pennsylvania and the trial's lead researcher, James M. Wilson, owned significant equity interests in the sponsor company, Genovo. Whether Gelsinger was informed of these financial interests remains a matter in dispute. Similarly, there remain questions surrounding Wilson's adherence to NIH regulations after Gelsinger's death, which require reporting adverse events.

⁵⁴ Department of Health and Human Services. 2001. Draft Interim Guidance - *Financial Relationships in Clinical Research: Issues for Institutions, Clinical Investigators, and IRBs to Consider When Dealing with Issues of Financial Interests and Human Subject Protection*. Washington D.C.: Health and Human Services. January 10, 2001, available at <<http://www.ohrp.osophs.dhhs.gov/nhrpac/mtg12-00/finguid.htm>>.

⁵⁵ *Id.*

⁵⁶ *Id.*

⁵⁷ *Id.*

⁵⁸ *Id.* at 1.1.

⁵⁹ *Id.* at 1.2.

⁶⁰ *Id.* at 1.6 and 1.7.

⁶¹ *Id.* at 1.8.

⁶² For a full list of items to be identified, see *id.* at 1.8.

⁶³ *Id.* at 2.2.

⁶⁴ *Id.*

⁶⁵ *Id.* at 1.3.

⁶⁶ *Id.* at 1.3 and 1.4.

⁶⁷ *Id.* at 1.5.

⁶⁸ *Id.* at 3.3.

⁶⁹ *Id.* at 3.1.

⁷⁰ *Id.* at 4.1.

⁷¹ *Id.* at 4.1.

⁷² *Id.* at 4.2.

⁷³ *Id.* at 4.3.

⁷⁴ *Id.* Section 4.3 also lists numerous additional questions that an IRB might consider in its deliberations regarding the financial interests of clinical investigators.

⁷⁵ *Id.* at 4.4.

⁷⁶ *Id.* at 5.2.

⁷⁷ *Id.* at 5.3.

⁷⁸ 793 P.2d 479, 483 (Cal. 1990), *cert. denied*, 499 U.S. 936 (1991).

⁷⁹ *Id.* at 483.

⁸⁰ *Id.*

⁸¹ *Id.* at 481.

⁸² *Id.* at 482.

⁸³ *Id.* at 486.

⁸⁴ *Id.* at 484.